New C–H Functionalization Reactions Based on Gold(I)/Gold(III) Redox Catalytic Processes

Dissertation

zur

Erlangung der naturwissenschaftlichen Doktorwürde

(Dr. sc. nat.)

vorgelegt der

Mathematisch-naturwissenschftlichen Fakultät

der

Universität Zürich

von

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Promotionskomitee

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Zürich, 2012

Acknowledgements

After these four years, it's my pleasure to thank those who made this thesis possible.

First of all, I would like to thank my supervisor Prof. Dr. Cristina Nevado for giving me the opportunity to carry out this thesis under her supervision. Without her generous support, enthusiasm, inspiration, persistence, encouragement and great efforts to explain things clearly and simply, this thesis wouldn't have been possible.

I am indebted to my master supervisors, Prof. Dr. Jose Luis Garcia Ruano and Prof. Dr. Belen Cid. They introduced me to the world of organic chemistry and provided me the direction to follow, encouraging me to do a PhD Thesis in this field. For their support and for believing in my skills I will always owe them my more sincere gratitude.

I would like to thank the Graduate School of Chemical and Molecular Science Zurich as well as all Organic Chemistry Institute members. In particular I thank Dr. Anthony Linden for the crystal structure determination and Dr. Laurent Bigler and his team for their great analytical work. I would also like to thank the administrative assistants Salomé Fässler and Dr. Christa Werner for helping me in many different ways. The organic chemistry institute and the Forschungskredit of University of Zurich are acknowledged for the financial support.

To Prof. Dr. Roger Alberto I would like to express my gratitude to being part of my promotionskomitee.

For the stimulating and fun environment, as well as for the helpful discussions and for their friendship I would like to thank all the members in Nevado's group. I am especially grateful to Olivia Roth, Karine Lafleur, Riccardo Cribiú, Maria Maluszynska-Hoffman, Martin Arthuis and Andrea Unzue for the fantastic time inside and outside of the lab. In addition, thanks go to Manuel Hofer and Pascal Feige who gave me the opportunity to teach them a bit of what I learnt during my PhD and for very interesting discussions.

And then all the other people who have made Zürich a very special place these years: Emma, Aglae, Ivona, Elitsa, Tina, Patrick, Thiago, Chris, Corjan, Raso, Ronaldo, Xinjun, Linglin, Silvia, Karla, Jaime, Blanca, Pedro, Bea, David and Ana.

I wish to thank my best Spanish friends, for helping me through the difficult times and for all the emotional support and caring they provided: Silvia, Pablo, Esti, Jorge, Ro, Tarta, Borja, Luis, Victor, Willy, Varo, Alberto, Prot, Jose, Elenita, Pini and Ana.

Despite the geographical distance, my family was always nearby. My brother César and my sister Mar provided me an unconditional love and support through this period of my life. My

parents made sure I felt their confidence and support, and their advice was consistently timely and useful. For supporting and loving me so much I will always be deeply grateful.

And last but not least I would like to thank David, ‘‘*my better half*’’, for his encouragement, his support and for loving me at every moment. None of this could have happened without him. This thesis is dedicated to him and to my family.

Foreword

This PhD thesis, except for Chapter 1, is based on the results published or going to be published in international scientific journals. Chapter 2, 4, 5 and 6 correspond to the papers in as much unchanged form of the respective manuscripts as possible. Therefore, compounds and references are number independently in each chapter.

The following publications have stemmed from this work:

1. **"Gold Catalyzed Ethynylation of Arenes"** de Haro, T.; Nevado, C. *J. Am. Chem. Soc*., **2010**, *132*, 1512–1513.

   DOI: 10.1021/ja909726h

2. **"Domino Gold-Catalyzed Rearrangement and Fluorination of Propargylacetates"** de Haro, T.; Nevado, C. *Chem. Commun*, **2011**, *47*, 248–249.

   DOI: 10.1039/c002679d

3. **"Gold Catalyzed Synthesis of α-Fluoroacetals and α-Fluoro-ketones from Alkynes"** de Haro, T.; Nevado, C. *Adv. Synth. Catal.*, **2010**, *352*, 2767–2772.

   DOI: 10.1002/adsc.201000559

4. **"Flexible Gold-Catalyzed Regioselective Oxidative Difunctionalization of Unactivated Alkenes"** de Haro, T.; Nevado, C. *Angew. Chem. Int. Ed.,* **2011**, *50*, 906–910.

   DOI: 10.1002/anie.201005763

Zusammenfassung

Direktes und selektives Ersetzen von Kohlenstoff-Wasserstoffbindungen durch C-C, C-O, C-N und C-F-Bindungen ist ein wichtiges und schon lange bestehendes Ziel der organischen Chemie. Diese Transformationen besitzen ein grosses Potential in der Synthese, da C-H-Bindungen in den meisten organischen Molekülen in grosser Zahl gefunden werden. Das Erreichen einer hohen Selektivität bei C-H-Bindungen mit unterschiedlicher Umgebung bleibt jedoch eine Herausforderung. In den letzten Jahren wurden für C-H-Funktionalisierungen, katalysiert durch Übergangsmetalle, erhebliche Fortschritte erzielt.

Gold hat sich als Metall der Wahl für die Aktivierung von C-C-Mehrfachbindungen erwiesen. Eine der interessantesten Eigenschaften von Gold ist seine Fähigkeit als milde, carbophile, π-Lewis-Säure zu reagieren. π-Bindungen, welche von Gold aktiviert werden, reagieren unter Anderem unter Addition von Nukleophilen, Umlagerungen von Propargylcarboxylaten oder Cycloisomerisationen. Oxidative Kopplungen, in welchen das Au(I)/Au(III)-Redoxpaar als Katalysator verwendet wird, wurden jedoch weniger entwickelt.

Diese Arbeit beinhaltet die Entwicklung neuer C-H-Funktionalisierungen auf Basis von Au(I)/Au(III) katalysierter Redoxprozesse. Die Bildung neuer C-C und C-Heteroatom-Bindungen soll den schnellen und effizienten Zugang zu komplexen Molekülen ermöglichen.

Der erste Teil befasst sich mit der Entwicklung einer goldkatalysierten Ethinylierung von Arenen via C-H-Funktionalisierung beider organischer Reaktanden, elektronenreicher Arene und elektronenarmer Alkine. Das Au(I)/Au(III)-Redoxpaar ist dabei verantwortlich für den katalytischen Umsatz. Eine detaillierte mechanistische Studie dieser Reaktion wurde durchgeführt.

Im zweiten Teil werden Kaskadenreaktionen, basierend auf einer Kombination von Gold als carbophile Lewis-Säure und oxidativer Kreuzkopplung zur Bildung von C-C, C-O, C-N und C-F-Bindungen entwickelt. In diesen Tandemreaktionen reagiert der Goldkatalysator in seiner traditionellen Rolle als redoxneutrale π-Säure und als Lieferant eines organischen Fragmentes. Auf der anderen Seite vermittelt der Goldkatalysator die Bildung der neuen C-C oder C-Heteroatom-Bindung durch oxidative Kopplung. Im weiteren wird eine goldkatalysierte, regioselektive Amionooxygenierung von nicht aktivierten Alkenen, eine neue Aminoamidierung durch Gold-Aktivierung von Nitrilen und eine Synthese zur Herstellung von trizyklischen 3-Benzazepinen, basierend auf einer goldkatalysierten, oxidativen Arylierung, entwickelt. Im letzten Teil wird eine effiziente Methode für die Synthese von α-Fluoroenonen, ausgehend von einfach zugänglichen Propargylacetaten und basierend auf einem goldkatalysierten Tandemprozess demonstriert. Im Weiteren wird die

goldkatalysierte Synthese von α-Fluoroacetalen und α-Fluoroketonen, ausgehend von Alkinen und unter Verwendung von stöchiometrischen Mengen Selectfluor als Fluorquelle, aufgezeigt.

Summary

Direct and selective replacement of carbon-hydrogen bonds with new C-C, C-O, C-N and C-F bonds represents an important and long-standing goal in organic chemistry. These transformations have an enormous potential in synthesis as C-H bonds are ubiquitous in organic molecules. In addition, achieving selectivity among many different C-H bonds also reminds a challenge. In the last years C-H functionalizations catalyzed by transition metals have progressed considerably, highlighting the potential of organometallic chemistry for useful C-H activation processes.

In recent times, gold has proven to be the metal of choice concerning the activation of multiple C-C bonds. One of the most interesting features is its ability to act as mild, carbophilic π-Lewis acid. π-Bonds activated by gold can undergo the addition of nucleophiles, rearrangement of propargyl carboxylates, or cycloisomerization reactions among other transformations. However, oxidative couplings in which the redox pair gold(I)/gold(III) is responsible of the catalyst, are less frequently disclosed.

The work described in this thesis is dedicated to the development of new C-H functionalization reactions based on gold(I)/gold(III) redox catalytic cycles for the construction of new C-C and C-heteroatom bonds to enable a rapid and efficient access to molecular complexity.

In the first part of this thesis a novel gold catalyzed ethynylation of arenes via C-H functionalization of both organic counterparts, electron rich arenes and electron deficient alkynes, is reported. The redox pair gold(I)/gold(III) is responsible for the catalytic turnover and a detailed mechanistic study of this transformation has been performed.

In the second part, cascade reactions based on the combination of gold as a carbophilic Lewis acid with oxidative cross-couplings enabling the construction of C-C, C-O, C-N and C-F bonds have been explored. In these tandem reactions, the gold catalyst first delivers the organic fragment by acting in its traditional role as a redox-neutral π-acid and then mediates the formation of a new C-C or C-heteroatom bond by oxidative coupling. A gold-catalyzed regioselective aminooxygenation of unactivated alkenes, a novel aminoamidation by gold activation of nitriles and a diastereomerically pure synthesis of tricyclic 3-benzazepines as a result of a gold-catalyzed oxidative arylation reaction have been achieved. Finally, an efficient method to synthesize α-fluoroenones based on a tandem gold-catalyzed process starting from easily available propargyl acetates and gold-catalyzed synthesis of α-fluoro acetals and α-fluoro ketones from alkynes using Selectfluor as the stoichiometric source of fluorine are also described herein.

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Introduction

1.1 A gold-rush era: an introductory perspective

Gold has been a topic that has fascinated humankind since it was first discovered. It is the most noble of the metals; it does not tarnish on exposure to the atmosphere and retains its beautiful luster undiminished for millennia. It has been the source of many wonderful historical artifacts and artworks and it is also a metal with high monetary value. Although it did fascinate alchemists before the advent of modern chemistry, gold has presented very little fascination for chemists until recently. The alchemists were convinced that metals were present in nature just as precursors of gold, as gold was considered to be the most perfect metal and nature always strives for perfection. The little interest in gold chemistry was due to its chemical inertness, as it was considered a 'dead entity' in terms of chemical reactivity.[1] In the last twenty years, the observation that gold can be exceptionally active as a catalyst has fostered a large number of discoveries both in homogeneous and heterogeneous catalysis.[2] Indeed gold fascinates now material scientists, surface, synthetic and computational chemists.

1.2 Carbophilic activation: basic concepts

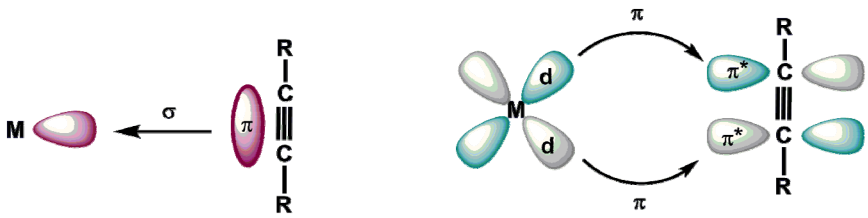
1.2.1 Structural aspects of alkynophilicity and π-acidity

Nowadays, the broadest and maybe most successful area in gold homogeneous catalysis stems from the carbophilicity of gold. This term is used to indicate the ability of gold to coordinate, and thus activate, triple and/or double bonds due to the strong relativistic effect governing its coordination behavior.[3]

The bonding situation in transition metal complexes with alkenes or alkynes as π ligands can be explained by the Dewar-Chatt-Duncanson (DCD) model,[4] which considers the bond as a donor-acceptor interaction between two closed-shell fragments.[5] Two major contributions in the plane of the bond are found: the first one stems from the overlapping between the π orbital of the ligand with an empty metal d orbital of suitable symmetry to form the σ bond. The second interaction occurs from a back-donation of electron density from a filled metal d orbital into an anti-bonding π* orbital of the unsaturated ligand. Usually, the σ donation dominates over the π back-bonding, thus indicating induction of partial positive charge on the ligand (Fig. 1). Indeed, any metal fragment that binds to a carbon-carbon multiple bond and thereby deprives it of part of its electron density, can be defined as a ''π acid''. Overall, π

acidic metal fragments can be regarded as the soft counterparts to the conventional Lewis acids.[6]

Figure 1. Orbital diagram showing the interaction between a metal and an alkyne ligand



The Dewar-Chatt-Duncanson model predicts an elongation of the double or triple bond as a consequence of the net shift of electron density from the bonding π orbital into the antibonding π* orbital. However, minor changes in the C-C bond length between the coordinated and the free ligand are observed. In addition, the C atoms in question present a near lineal or near trigonal coordination geometries for alkyne and alkene respectively, with low degrees of rehybridation. Due to the overall depletion of electron density, the alkyne or alkene ligand, is susceptible to nucleophilic attack to form alkenyl- or alkyl metal complexes respectively.

Computational studies have showed that ethylene is a slightly better σ-donor than acetylene.[7] However, in polyunsaturated substrates, such as enynes, it is unlikely that the gold complex will distinguish between the different π systems. Nevertheless, in many of the gold(I)-catalyzed processes a high selectivity towards the alkyne moiety has been observed which is supposedly kinetic in origin. In other words, the pronounced ‘‘alkynophilicity’’ of noble metals likely reflects the preference of the nucleophile to attack the coordinated triple bond. Furthermore, electrostatic contributions are also essential in the bonding situation. Computational analysis have indicated that electrostatic interactions between the ligand and metal template [M^+ (C_2H_4) and M^+ (C_2H_2) M = Cu, Ag, Au) play an important role in the total bonding force.[7b,8]

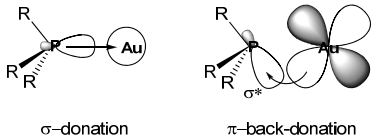
1.2.2 Gold(I) and gold(III) complexes for activation of unsaturated C-C bonds

Simple commercially available gold salts such as $NaAuCl_4$, $AuCl_3$, $AuBr_3$ or AuCl are active enough to catalyzed nucleophilic additions to alkynes. Nevertheless, these gold(III) salts are quickly reduced to inactive metallic gold(0), and AuCl tends to disproportionate to metallic gold and gold(III) chloride in an autoredox reaction.[9] Most carbophilic activation studies by gold(I) employ chloride complexes bearing a monodentate ancillary ligand [LAuCl] that usually needs to be activated by abstraction of the chloride using silver salts with a non-coordinating anion. Upon chloride abstraction, a mono-ligated cationic catalyst is generated.

To stabilize cationic gold(I), donor ancillary ligands such a phosphines or carbenes are commonly used.

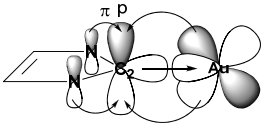
In the case of phosphines, the lone pair of the phosphorous atom of the PR_3 ligand donates electron density to the empty d orbital of the transition metal and a filled d orbital of the metal back-donate electron density to the empty P-R σ* orbital (Fig. 2). The overlapping between the P-R σ* orbital and the d-orbital of the metal depends on the electronegativity of the R groups attached to the phosphorous atom increasing with the more electron-demanding R groups.[10]

Figure 2. Orbital diagram showing the interaction between a metal and a phosphine ligand



On the other hand, the use of *N*-heterocyclic carbenes (NHCs) as ancillary ligands affords stable gold carbene complexes where the lone pair of the NHC acts as a donor to the metal. Additionally, an empty p orbital at C_2 acts as acceptor for the lone pairs of the nitrogen atoms as well as for the small back donation from a filled d orbital of the metal (Fig. 3).This π bonding interaction disfavor triple carbene and therefore, the NHC bonding can be considered a Fisher carbene type.[10,11]

Figure 3. Orbital diagram showing the interaction between a metal and a NHC-carbene ligand



Different types of gold(I) complexes bearing bulky, biphenyl-based phosphines, phosphites or NHC ligands lead to very active catalyst in the carbophilic activation of double and triple bonds. Although gold(III) complexes have been also developed, such precatalysts are more limited due to their propensity to increase byproducts generation and ability to reduce to gold(0). Gold(III) complexes containing bidentate 2-pyridine carboxylate ligands have proved to be an exception developing as ideal ligands to promote activation of unsaturated C-C bonds.[2,3]

1.3 Gold-catalyzed C-H activation processes

Most organic compounds contain at least one of the three standard C-H bonds: Csp^3-, Csp^2- or Csp-H. The ubiquitous nature of carbon-hydrogen bonds in organic molecules offers an unparalleled platform for the development of new reactions while posing reactivity challenges

that still remain to be solved in the XXI century. On one hand, if C-H bonds could be used as operative functional groups, the efficiency, atom-economy and cost effectiveness of organic transformations would be immediately increased.[12] However, such an ideal scenario is hampered by the low reactivity and high thermodynamic stability of these bonds, with dissociation energies (BDE) up to 115 kcal/mol. It is thus not surprising that their selective activation in the presence of other, likely much more reactive functional groups, is far from trivial.

It is important to mention the different between C-H activation and C-H functionalization. C-H bond activation involves the scission of a C-H in favor of a C-metal bond, which is commonly followed by functionalization.[13] The term C-H bond functionalization is more general and is applied to transformations where cleavage of a C-H bond is followed by new bond formation at the carbon center.[14] Stoichiometric cleavage of C-H bonds by transition metals has been extensively studied since 1960s.[15] In contrast, the catalytic C-H bond functionalization[16] of organic molecules, which offers a huge synthetic potential to build complex structures, is still in developmental phases. In the reported gold examples that will be discussed in the following section, the exact nature of the C-H activation event is rather difficult to specify. Classical mechanisms such as oxidative addition, addition to electrophilic metal center, σ-bond metathesis, reversible addition to an M=X bond, or radical processes have been invoked but further mechanistic work is needed in this rapid-developing area.[17]

1.3.1 Gold catalyzed C_{sp}-H activation processes

The interaction of gold species with alkynes is rather prolific. As described above, due to its soft Lewis acidity, gold seeks π-electron density increasing the electrophilic character of the alkyne upon coordination, thus enabling the attack of nucleophiles in an intra- or intermolecular manner.[3] Additionally, in such π-alkyne-metal complexes, the σ-contribution to the bond pulls away electron density from the triple bond, increasing the acidity of the Csp-H bond and facilitating the C-H activation process with the concomitant formation of gold acetylides. These new species can either react as organometallics in nucleophilic addition and substitution reactions, or can participate in catalytic redox process, in analogy to copper acetylides.

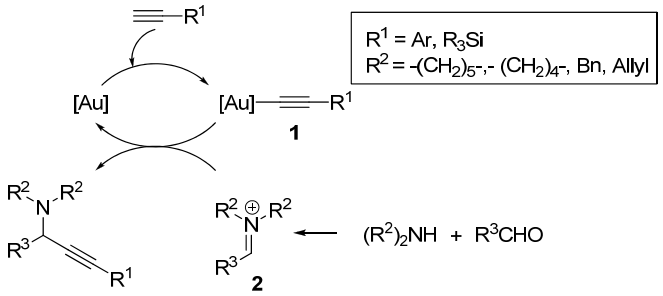
In a stoichiometric form, gold(I)- and gold(III)-acetylide species can be prepared either by reaction of terminal alkynes with a suitable gold complex [LAuCl] in the presence of a strong base in the former case[18] or, in the latter, by substitution of the halogen ligand in *cis*-Me_2(L)AuX with lithium acetylides respectively.[19] In a recent work, Nolan and co-workers reported a new route to access NHC-gold(I) acetylenes from the air stable synthon [Au(OH)(IPr)] and terminal or trimethylsilyl-protected alkynes. The OH group of the initial

gold-complex is able to abstract either the proton or the silyl group of the alkyne to give the corresponding IPrAuC≡CR complexes.[20]

1.3.1.1 Gold acetylides as nucleophiles

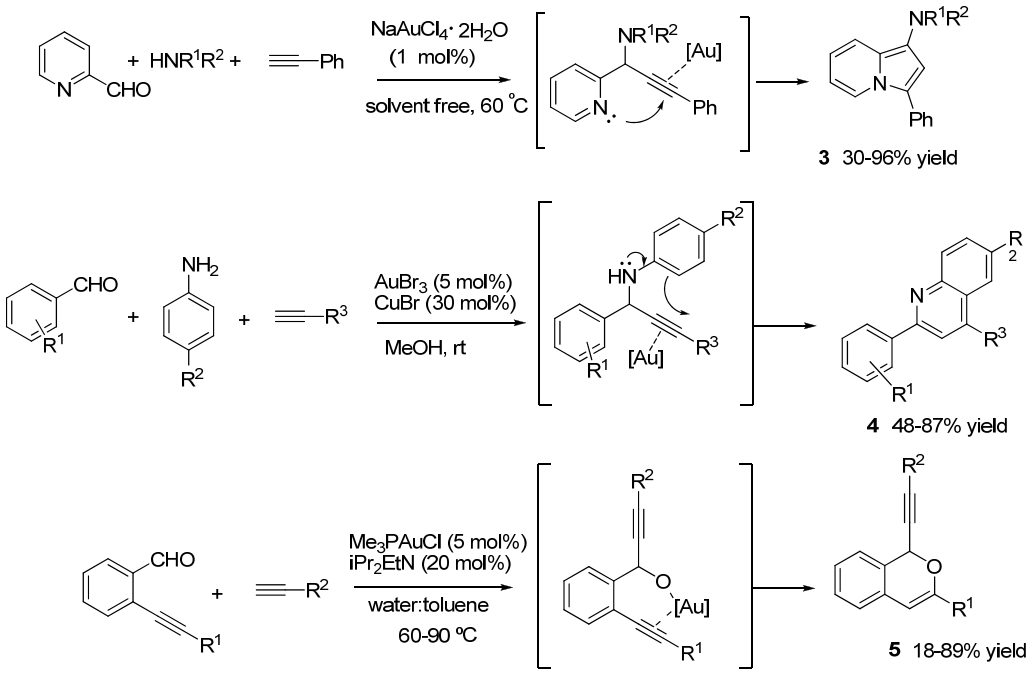
The nucleophilicity of gold acetylides has been exploited to form C-C bonds under catalytic conditions. In 2003, Li and co-workers reported the use of gold acetylides in the synthesis of propargylamines by a multi-component reaction between aldehydes, terminal alkynes and secondary amines. The coupling proceeds in the presence of gold(I) and gold(III) salts in water, although in the latter case, a reduction to gold(I) species is proposed. The authors suggest a mechanism involving the C-H activation of the terminal alkyne to form gold acetylide species **1**, which react with iminium ion **2**, generated in situ from the condensation of the aldehyde with the secondary amine (Scheme 1).[21] When chiral amines such as prolinols were used, this transformation proved to be highly diasteroselective using gold(III)-salen catalysts.[22] These transformations have been also reported to proceed in a heterogeneous fashion using gold nanoparticles and layer double hydroxide-supported gold (LDH-$AuCl_4$).[23] A related reaction, the A^3 coupling between terminal alkynes, aldehydes and triethyl orthoformate in the presence of catalytic amounts of $Ph_3PAuOTf$, provides access to propargyl ethers in high yields.[24]

Scheme 1. Gold-catalyzed three-component coupling of aldehydes, alkynes and amines



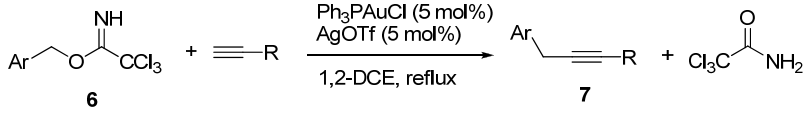
Several synthetically useful applications of this methodology have been devised by combination with a subsequent nucleophilic addition onto the metal-activated alkyne. Aminoindolizines **3**,[25] quinolines **4**,[26] and 1-alkynyl-1H-isochromenes **5**,[27] can be efficiently obtained as summarized in Scheme 2.

Scheme 2. Synthetic applications of gold-acetylide intermediates



Gold acetylides can also be used as intermediates in substitution reactions. Benzyl trichloroacetimidates **6** were substituted by *in situ* generated gold-acetylides leading to benzylacetylene products **7** in good yields (Scheme 3).[28] The nucleophilic character of gold acetylides has been further exploited in the synthesis 1-halo-alkynes using *N*-halo succinimides.[29]

Scheme 3. Gold-acetylide intermediates in substitution reactions



1.3.1.2 Gold acetylides in oxidative cross coupling reactions

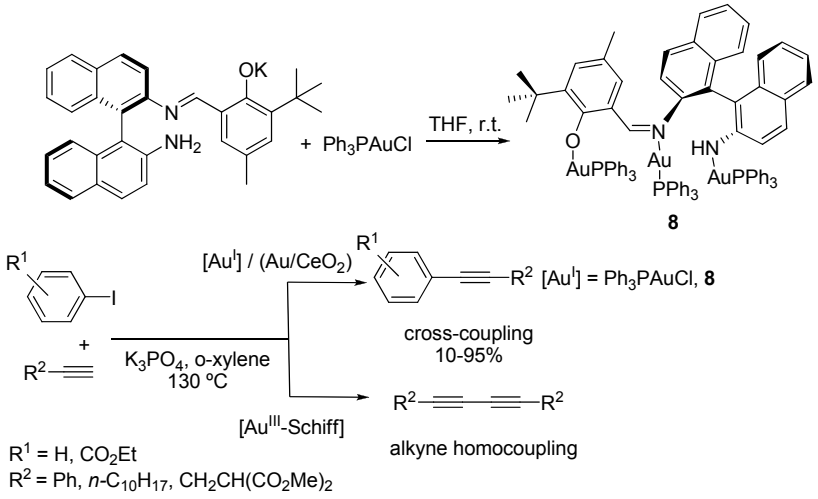
An extensively used synthetic method involving metal-catalyzed alkyne activation is the Sonogashira cross-coupling reaction.[30] Typically palladium and copper are used as catalysts, copper being responsible for the alkyne activation and subsequent transmetalation to the organopalladium(II) intermediate.

Many variations of this reaction have been reported up to date, some of them focused in the development of new co-catalyst as an alternative for copper. In 2007, Laguna and co-workers replaced copper for gold(I) and gold(III) salts in the Sonogashira reaction.[31] Although the reaction times were slightly longer than with CuI, the use of a gold co-catalyst provided

cleaner reactions, avoided homocoupling products and allowed the use of technical grade solvents without previous purification or air exclusion.

A step further was achieved with the replacement of both palladium *and* copper for gold as reported by Corma and co-workers using either gold metal nanoparticles supported on nanocrystalline ceria (Au/CeO_2) or mononuclear salts such as Schiff-base gold(I)- (**8**) or commercially available Ph_3PAuCl (Scheme 4).[32] gold(III)-complexes seemed to catalyze the undesired alkyne homocoupling whereas gold(I)-salts seemed to be responsible for the formation of the desired alkynylation products. Antunes and co-workers also used gold supported catalysts under microwave irradiation to effect this transformation.[33] Finally, Wang and co-workers reported a tandem Sonogashira/cycloisomerization reaction of 2-amino-1-haloarenes with terminal alkynes to give indoles using gold(I) iodide catalyst with the bidentate dppf ligand[34] in 1 : 1 molar ratio.[35]

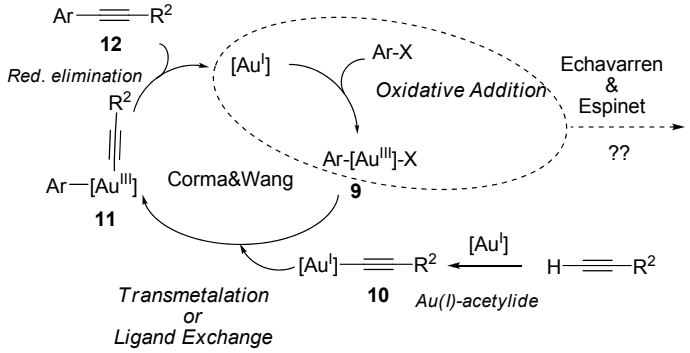
Scheme 4. Gold-catalyzed Sonogashira-type cross-coupling reaction



The proposed mechanism in the above-mentioned transformation invokes the commonly accepted steps for Pd-catalyzed processes in which oxidative addition on the aryl halide occurs on gold(I) species thus generating a gold(III)-intermediate **9**. Upon transmetalation with a gold acetylide **10** and reductive elimination on intermediate **11**, the aryl alkynes **12** were obtained (Scheme 5). However, Echavarren and Espinet,[36] and Lambert[37] recently proved the inability of gold(I) mononuclear complexes to undergo an oxidative addition process. Careful experimental work showed that indeed, traces of Pd present even in the commercially available gold sources could be responsible of the observed cross-coupling products, as addition of small amounts of Pd to the gold-catalyzed reaction increased the yield in the Sonogashira product. In a latter communication,[38] Corma aimed to reconcile both set of results suggesting that the mononuclear gold(I) complexes react merely as pre-catalysts being the *in situ* generated gold nanoparticles in solution the real catalysts of the Sonogashira

reaction. The activation energy for the oxidative addition on the aryl halide is much lower for these species compared to mononuclear complexes. At this stage, further experimental work might be necessary to assure the reproducibility of the reaction when mononuclear gold(I) complexes such as Ph_3PAuCl or **8** are used.

Scheme 5. Proposed reaction mechanism for the gold-catalyzed Sonogashira-type cross-coupling reaction



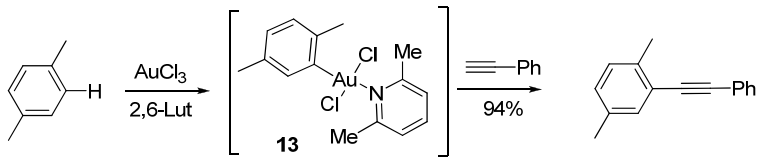
1.3.2 Gold catalyzed Csp^2-H activation processes

The activation of arenes by gold(III) salts was established at the beginning of the past century. However, the activation by gold(I) complexes and the further functionalization of the arene to form new Csp^2-C and Csp^2-X bonds (X = heteroatom) has mainly aroused in the last ten years. As was mentioned in the introduction, not all the gold- mediated functionalization processes entail a Csp^2-H activation step. Due to the well known π-acidity of gold, a Friedel-Crafts type mechanism can explain the formation of the observed products in most of the reported cases.

1.3.2.1 Csp^2-H bond activation by gold(III)

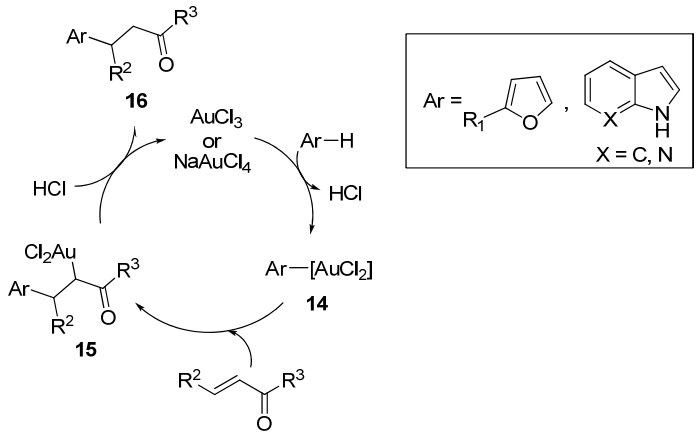
The first activation of arenes in the presence of stoichiometric amount of gold(III) was reported in 1931 by Kharasch and Isbell.[39] It's commonly accepted that the reaction proceeded through an electrophilic aromatic substitution process.[40] However, the use of this new methodology to functionalize aryl compounds was not investigated in depth until 2001. In the presence of stabilizing ligands such as 2,6-lutidine, Fuchita and co-workers were able not only to isolate and characterize complexes such as **13**, but also achieved the further functionalization of the aromatic ring by cross coupling reaction with phenyl acetylene (Scheme 6).[41]

Scheme 6. Stoichiometric gold-arylation of alkynes via Csp^2-H activation



The gold(III)-catalyzed addition of electron rich aromatic rings to *α,β*-unsaturated carbonyl compounds has been widely investigated. It is commonly proposed that the first step in these transformations involves the auration of the aromatic counterpart **14** followed by carbometalation of the enone system in a 1,4-Michael type addition to give **15** (Scheme 7). Final protodemetalation affords the observed products **16**.

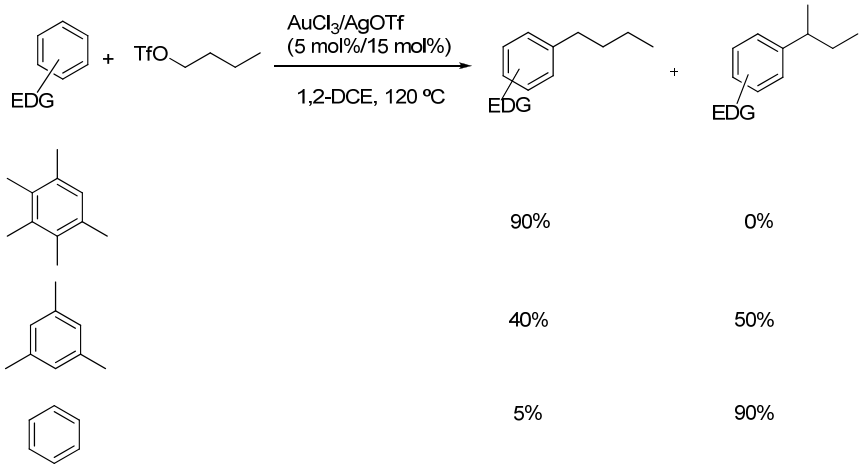
Scheme 7. Gold-catalyzed addition of electron-rich arenes to enones via Csp^2-H activation



The addition of furans to *α,β*-enones, was first reported by Hashmi[42] and further developed by Urriolabeitia and Contel.[43] In the case of furanes, stoichiometric amounts of $AuCl_3$ were mixed with 2-methylfuran and the reaction monitored by ^{1}H-NMR spectroscopy. The resonance of the proton at the C_5 disappeared and those of the hydrogen atoms at the C_3- and C_4- positions appeared broadened supporting a furan auration at C_2- as first step of the catalytic cycle.[44] The addition of indoles[45] and azaindoles[46] onto *α,β*-unsaturated carbonyl compounds using $NaAuCl_4 \bullet H_2O$ was reported by Arcardi and co-workers. Although the Friedel-Crafts-type mechanism cannot be ruled out, the authors propose a direct electrophilic attack of gold(III) at the C_3- position of the indole. The detection of the arene aurated species [indole-AuCl]$^+$ by mass spectrometry (ESI-MS) in a mixture of indole with stoichiometric amount of $NaAuCl_4 \bullet H_2O$ in MeCN support the C-H activation hypothesis. The addition of indoles, furans and arenes to electron deficient as well as unactivated alkenes and alkynes has also been further investigated by He[47] and Reetz.[48] In these cases though, the auration of the aromatic counterpart could not be demonstrated. A direct functionalization of arenes with primary alcohol sulfonate esters catalyzed by gold(III) was reported by He and co-workers in

2004.[49] The authors observed two different mechanisms depending on the electronic demand of the aromatic counterpart. Electron-rich arenes undergo S_N2 type mechanism involving an arylgold(III) intermediate to lead linear products whereas benzene or other less electron-rich arenes react by a classical Friedel-Crafts pathway to form branched products (Scheme 8).

Scheme 8. A gold-catalyzed Csp^2-Csp^3 bond formation via Csp^2-H activation

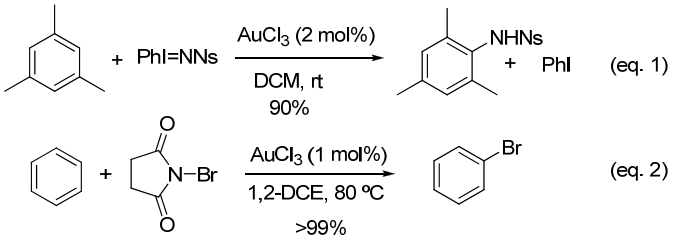


To support this hypothesis dichlorophenylgold(III) complex was prepared and treated with 2 equiv. of AgOTf and 2 equiv. of *n*-butyl triflate. After 2 days 30% of the linear product was detected and 70% after 7 days. Interestingly, no branched product was formed. Further evidence of a Csp^2-H activation process was obtained in the reaction of pentamethylbenzene, which could be transformed into chloropentamethylbenzene by adding saturated aqueous NaCl solution. The chlorinated product is likely to arise from an arylgold(III) intermediate formed during the reaction upon treatment with the aqueous NaCl solution.

The ability of gold(III) to metalate aromatic Csp^2-H bonds has also been exploited in the formation of Csp^2-N and Csp^2-Br bonds. In 2007, He and co-workers reported a gold(III)-catalyzed nitrene insertion into aromatic and benzylic C-H bonds using [(nosylimino)iodo]benzene (PhI=NNs) (Scheme 9, eq. 1).[50] The fact that other metal ions were not effective under the same reaction conditions and the disappearance of the proton signal from both the aromatic and the benzylic position in the ^1H NMR spectrum when a mixture of 1,3,5-triisopropylbenzene and stoichiometric amount of $AuCl_3$ in CCl_4 was quenched with D_2O, suggested that a C-H activation process was taking place during the reaction mechanism. Four years later, Zhang and co-workers reported a $AuCl_3$ catalyzed amination of arenes using azodicarboxylates.[51] Under mild conditions not only electron rich arenes but also electron-deficient ones could be aminated. In 2010, Wang and co-workers developed a gold(III)-catalyzed bromination of aromatic substrates with *N*-bromosuccinimides (NBS).[52] The authors proposed a double activation of both the arene and

NBS reagent based on the low reactivity of other Lewis acids and also labeling experiments (Scheme 9, eq. 2).

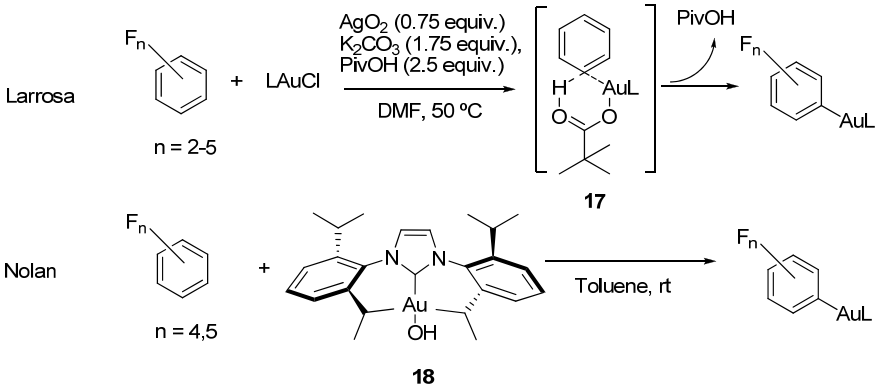
Scheme 9. A gold(III) catalyzed Csp^2-N and Csp^2-Br formation via Csp^2-H activation



1.3.2.2 Csp^2-H bond activation by gold(I)

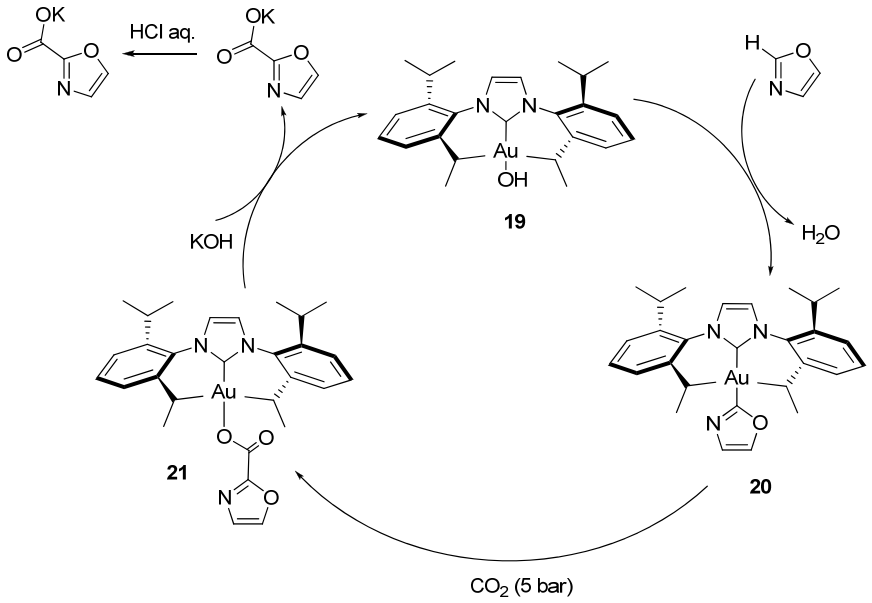
Recently, gold(I) salts have also been shown to perform Csp^2-H activation of electron poor arenes. Larrosa[53] and Nolan[54] simultaneously reported the synthesis of polyfluoroarylgold(I) complexes (Scheme 10).

Scheme 10. Gold(I)-catalyzed Csp^2-H activations



In contrast to the selectivity observed in gold(III)-mediated Csp^2-H activations, electron-deficient aromatic rings are favored over the electron-rich ones. In Larrosa´s case, strong σ-donor ligands afforded better yields of the aryl-aurated species. Due to a large primary kinetic isotopic effect (KIE = 5.0), the scission of the C-H bond seems to be the rate determining step. A concerted metalation-deprotonation reaction is proposed in which a coordinate pivaloate ligand acts as a proton acceptor via a six-member ring transition state **17**. On the other hand, Nolan and co-workers reported the synthesis of N-heterocyclic carbene gold hydroxide **18** and its ability to afford C-H activation in the synthesis of arylgold(I) complexes in the absence of silver salts and bases, highlighting the strong basicity of this complex. The reaction only works with tetra and pentafluorobenzene. This carbene gold(I) complex has been proved to catalyze the carboxylation of electron poor aromatic heterocycles and arenes with high regioselectivity at the most acid C-H bond position (Scheme 11).[55]

Scheme 11. IPrAu-OH catalyzed Csp^2-H activations of oxazoles



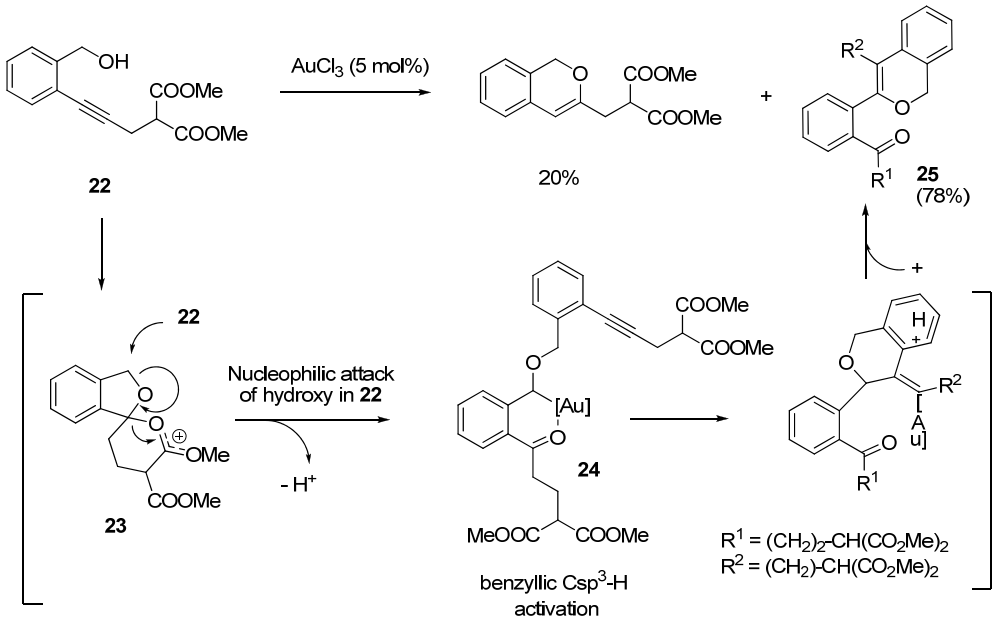
The mechanism, studied using oxazole as starting material, is proposed to begin with the C-H activation of the heterocycle to form intermediate **20** followed by insertion of CO_2 at the Csp^2-Au bond leading to intermediate **21**. Finally upon metathesis of **21** with KOH and subsequent acid hydrolysis the oxazole-2-carboxylic acid is obtained. This proposal is supported by the isolation of all the proposed intermediates, which proved to be active in the carboxylation reaction.

1.3.3 Gold catalyzed Csp^3-H activation processes

Due to the large bond dissociation energy, the low proton acidity and the high non polar character of the Csp^3-H bond, the C-H activation of saturated hydrocarbons in a mild and selective manner is still an unconquered holy grail.[56] Although effective methods for the catalytic activation of C-H bond in alkanes are still rare,[57] gold has proved to be a promising catalyst for the development of these transformations.

In 2007 Hashmi and Laguna reported a gold-catalyzed benzylic Csp^3-H activation that takes place under neutral conditions at room temperature (Scheme 12).[58] During the ring closure of alkynyl benzylic alcohols (**22**), the authors observed that substrates bearing additional nucleophilic groups like ester or amides afford not only 6-*endo*-dig cyclization products but also an unexpected dimmer **25** in which eight new bonds have been formed.

Scheme 12. Gold-catalyzed activation of benzylic Csp^3-H bonds

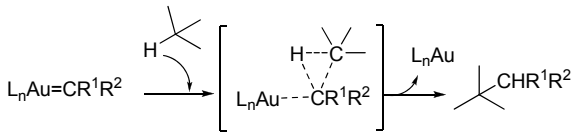


The proposed reaction pathway for this transformation starts with a nucleophilic addition of the carbonyl ester group onto the activated alkyne followed by intramolecular addition of the hydroxyl moiety affording tricyclic intermediate **23**. The hydroxyl group of a second molecule of **22** performs the ring opening of the system to afford the corresponding ether which then undergoes electrophilic Csp^3-H activation at the benzylic position forming a C-Au bond. The C-metal bond is stabilized by coordination/chelation with the adjacent carbonyl group (**24**). Upon protonolysis and isomerization of the double bond, the corresponding dimmer **25** is formed. The direct α-auration of acetone, characterized by X-Ray when trying to recrystallize [(Mes_3P)PAuX] in acetone, supports the C-H activation mechanism in this transformation.

1.3.3.1 Csp^3-H activation by means of gold-carbene induced C-H insertion

Functionalization of unactivated Csp^3-H bonds by insertion onto a gold-carbene has also been demonstrated.[59] In this case, the metal atom is thought not to interact directly with the alkane Csp^3-H bond (Scheme 13).

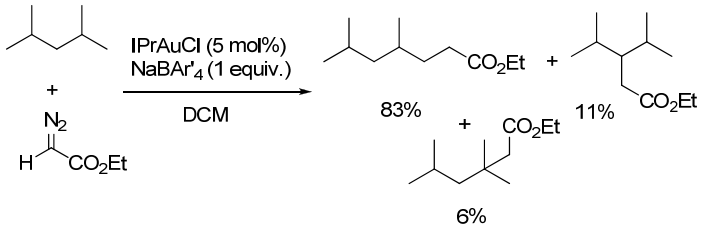
Scheme 13. Gold- carbene induced C-H activation



Gold carbenes generated *in situ* from diazo compounds insert into Csp^3-H bonds as investigated by Nolan and Pérez.[60] A cationic $[IPrAu]^+$ catalyst promotes the functionalization

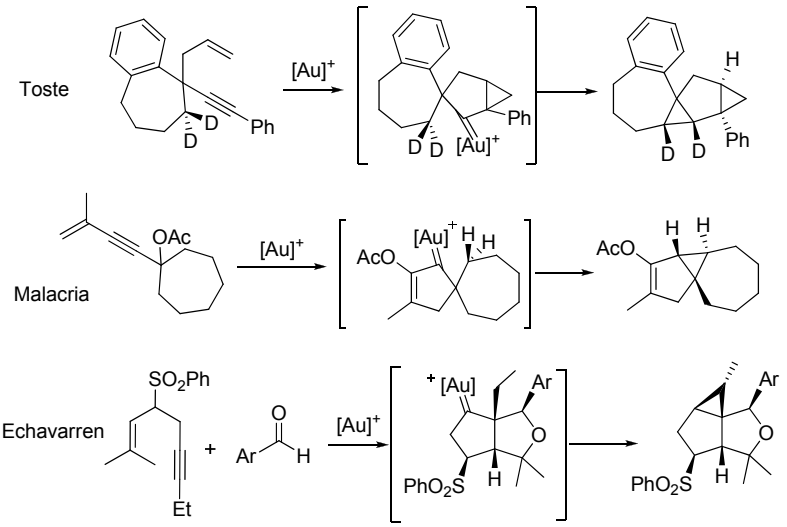
of primary C-H bonds whereas when IPrCu-catalyst is used the opposite regioselectivity is obtained (Scheme 14). Furthermore, the regioselectivity reached with this gold-based system is higher than those reported with rhodium or silver.

Scheme 14. Gold-carbene induced C-H activation



Cationic gold salts have also shown to promote cycloisomerizations terminated by Csp^3-H bond insertion into a gold carbene. In these reactions the gold catalyst activates the alkyne towards nucleophilic addition but also stabilizes the cationic intermediate produced in the cyclization, forming the gold-carbene intermediate that evolves via C-H insertion process. In 2009, Toste,[61] Malacria[62] and Echavarren[63] exploited such tandem processes in the synthesis of complex polycyclic scaffolds as summarized in Scheme 15.

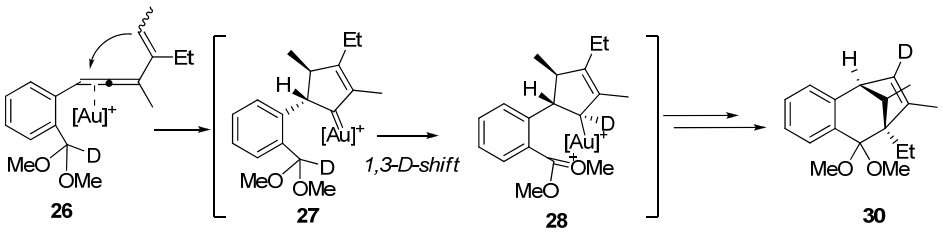
Scheme 15. Gold-catalyzed cycloisomerization/Csp^3-H bond functionalization



In the cycloisomerization of allene-acetal **26** catalyzed by cationic gold(I) species to form bicyclo[3.2.1]oct-6-en-2-ones **30**, an unprecedented 1,3-addition of a Csp^3-H bond to a vinylcarbene **27** was proposed by Liu and co-workers (Scheme 16).[64] On the basis of deuterium labeling and cross over experiments, it was suggested that the cleavage of the D-$C(OMe)_2$ bond in **27** proceeds through an intramolecular hydride transfer, induced by the gold carbenoid carbon to form gold(I)-η^1-allyl complex **28** containing a dimethoxy oxonium cation.

In fact, the 1,3 hydride transfer seems to be facilitated by the methoxy groups through its coordination to carbenoid carbon.

Scheme 16. Gold-catalyzed cycloisomerization/1,3-H shift



1.4 Gold(I)/gold(III) redox catalytic cycles for C-C and C-heteroatom oxidative coupling.

Formation of C-C and C-X (X= heteroatom) is one of the most important transformation in organic synthesis. In the last decades, late transition metal catalyzed cross coupling reaction have emerged as one of the best and simplest method in the direct coupling for the synthesis of these ubiquitous bonds.[65] In particular, palladium-catalyzed Csp^2-Csp^2 bond forming reactions such as Heck, Suzuki, Negishi and Sonogashira among others, have been the method of choice for the construction of C-C bond being recently recognized with the Novel Prize in Chemistry 2010.[66] Although palladium has received the most attention, other metals such as nickel, iron, and copper among others also present similar reactivity.[64] The mechanism of the cross coupling reactions involves an oxidative addition step of aryl halide or triflates proceeding through M(n)/M(n+2) redox catalytic cycles.

The use of gold in cross coupling reaction has been less widely explored due to the high redox potential of gold(I)/gold(III) couple (E_0 = + 1.41 V)[67] which make the oxidative addition an unfavorable process. Although Suzuki and Sonogashira reactions catalyzed by gold has been proposed,[32,33,35] as was mentioned in the section 1.3.2, the involvement of gold(I)/gold(III) redox catalytic cycles has been questioned.[36,37]

During the development of this thesis, we and others have demonstrated that an alternative approach to achieve gold(I)/gold(III) redox catalytic cycles is to use an external oxidant to perform the oxidation process (Scheme 17, fig. a). This method has shown to be very efficient as the coupling counterparts do not need to be prefunctionalized in most cases due to the ability of gold to undergo C-H activation processes (Section 1.3).[68]

Additionally, gold-catalyzed nucleophilic additions onto activated C-C triple and double bond followed by the oxidative coupling by gold(I)/gold(III) redox catalytic cycles has been successfully demonstrated, replacing the protodeauration step typically observed in gold-catalyzed alkyne, allene or alkene hydrofunctionalization reactions (Scheme 17, fig. b).[68]

Scheme 17. Representative mechanisms of gold(I)/gold(III) redox catalytic cycles

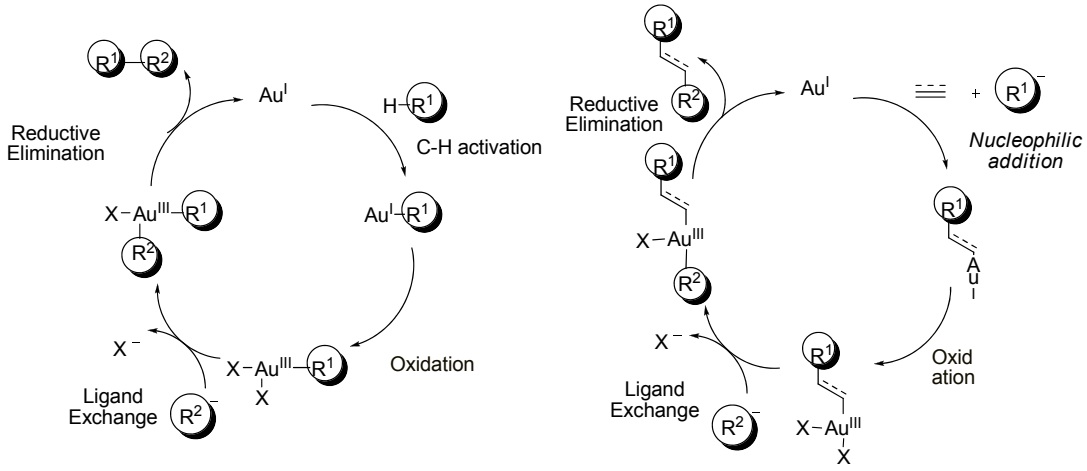


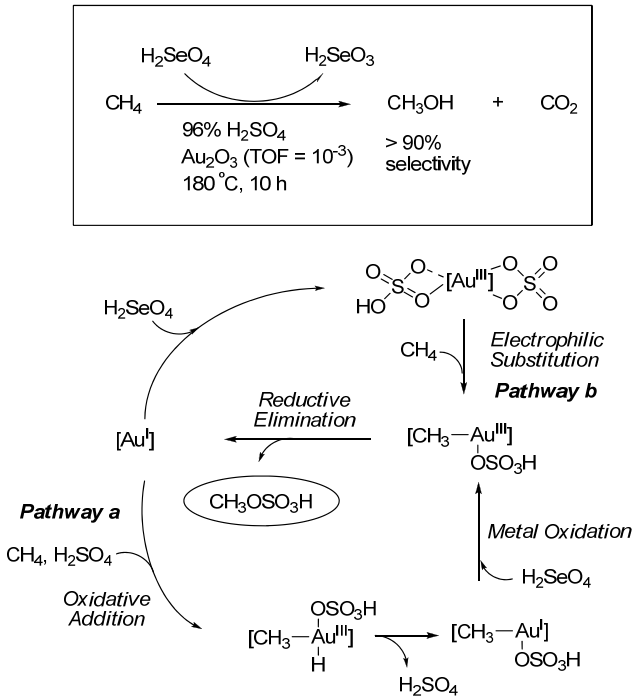
Fig. a. C-H activation followed by Au(I)/Au(III) redox catalytic cycles

Fig. b. Nucleophilic addition onto C-C multiple bond followed by Au(I)/Au(III) redox catalytic cycles

1.4.1 Gold(I)/gold(III) catalysis: C-O oxidative coupling

The first successful example where gold(I) was oxidized to gold(III) in a catalytic reaction was reported by Periana and co-workers in 2004. A selective and high yielding oxidation of methane to methanol was developed using cationic gold complexes in concentrated sulfuric acid with Se(VI) ions as the stoichiometric oxidant (Scheme 18).[69]

Scheme 18. Gold-catalyzed activation of Csp^3-H bonds

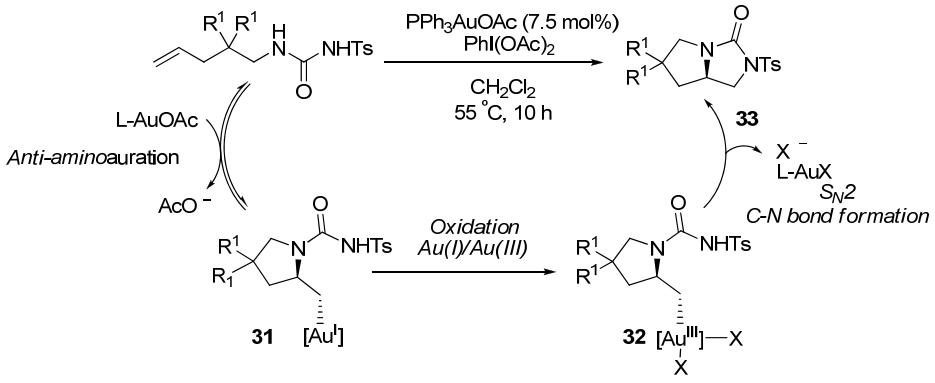


Based on both experimental and computational studies, the proposed catalytic cycle involves the formation of CH_3-Au(I) species, oxidation of the metal, and reductive elimination, although the order of these events might depend on whether methane is activated on gold(I) by oxidative addition (Scheme 18, pathway a) or on gold(III) by electrophilic substitution (Scheme 18, pathway b). Although the majority of gold is present as gold(III), a reaction starting with oxidative addition of CH_4 on gold(I) seems to be energetically favored and cannot be ruled out.

1.4.2 Gold(I)/gold(III) catalysis: C-N oxidative coupling

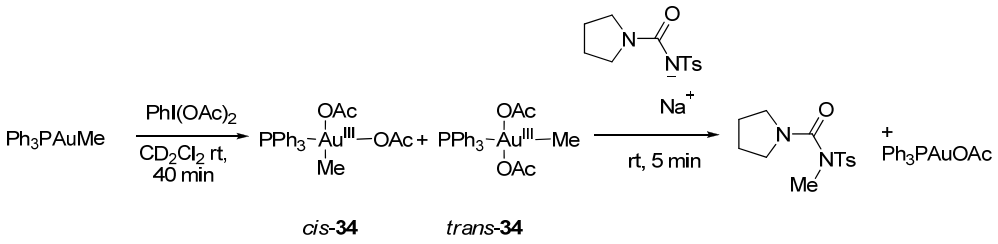
In 2009 Muñiz and co-workers reported a gold-catalyzed intramolecular diamination of alkenes related to those based on Pd(II)/Pd(IV) catalytic cycles.[70] The experimental study of the individual steps along the catalytic cycle indicates that the formation of *trans-5-exo*-aminoaurate intermediate **31** upon activation of the olefin by the gold complex occurs at metal oxidation state +I. Oxidation takes place to form gold(III)-alkyl species **32** followed by an intramolecular alkyl–nitrogen bond formation via S_N2 reaction, in which gold(III) behaves as a leaving group (Scheme 19).

Scheme 19. Diamination of unactivated alkenes



Spectroscopic evidence for the oxidation of gold(I) to gold(III) by $PhI(OAc)_2$ was provided by treating Ph_3PAuMe with the oxidant in CD_2Cl_2. This reaction led two new species in a 9:1 ratio which could be identified by NMR spectroscopic analysis as the *cis* and *trans* isomers of the gold(III) complex **34** (Scheme 20). The addition of a nitrogen nucleophile to this mixture afforded the *N*-methyl urea and the gold(I) species $Ph_3PAuOAc$. Acetylated products resulting from C-O reductive elimination were not observed, implying that the acetate groups act as spectator ligands.

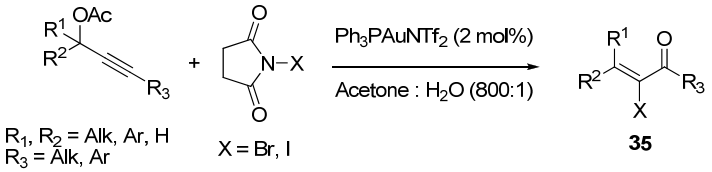
Scheme 20. Oxidation of Ph_3PAuMe with $PhI(OAc)_2$



1.4.3 Gold(I)/gold(III) catalysis: C-halogen oxidative coupling

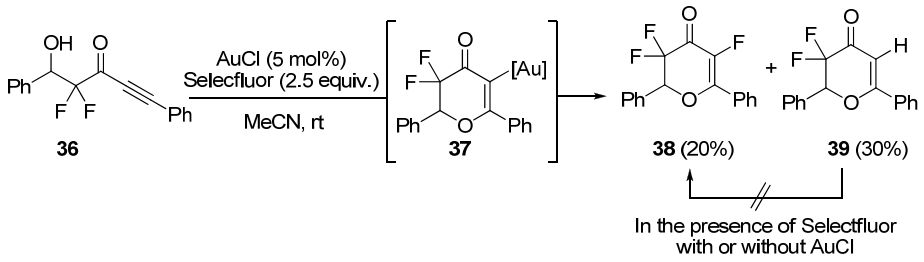
There are few examples in the literature where the formation of a C-halogen bond occurs by a gold(I)/gold(III) redox catalytic cycles or by halodeauration reaction. Thus, synthesis of *Z*- and *E*-*α*-haloenones (**35**) from readily accessible propargylic acetates and alcohols was reported by Zhang and coworkers (Scheme 21).[71]

Scheme 21. Gold triggers synthesis of *Z* and *E*-*α*-haloenones



The second example was reported by Gouverneur[72] in the gold(I)-catalyzed alkoxyfluorination of ynones **36**. The *6-endo-dig* cyclization of the difluorinated substrates conducted in the presence of gold and Selectfluor afforded trifluorinated dihydropyranone (**38**). However protonation of intermediate **37** becomes a competitive process in this case diminishing the synthetic utility of the process (Scheme 22).

Scheme 22. Gold(I)-catalyzed alkoxyfluorination of ynones



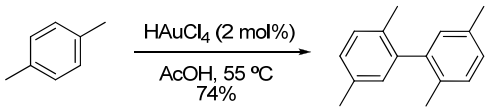
1.4.4 Gold(I)/gold(III) catalysis: C-C oxidative coupling

1.4.4.1 Oxidative coupling reactions involving Csp^2-H functionalization

In 2008 Beller and Tse reported the homocoupling of simple arenes in the presence of tetrachloroauric acid as catalyst and $PhI(OAc)_2$ as stoichiometric oxidant.[73] As an example, 1,4-dimethylbenzene reacts to give 2,2',5,5'-tetramethylbiphenyl in 74% isolated yield

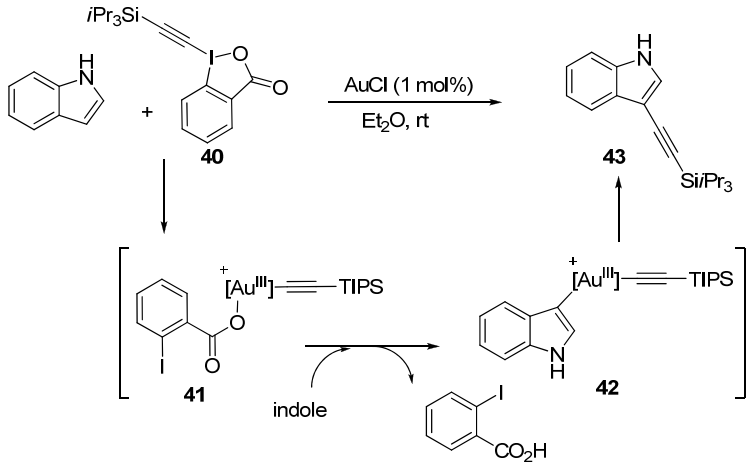
(Scheme 23). Interestingly the reaction requires an acidic solvent and does not require any silver salt to enhance the reactivity. The authors proposed that the reaction proceeds *via* a double C-H functionalization, which is in principle the most efficient process for the synthesis of biaryls, being gold(III) the active catalytic redox state. A typical electrophilic aromatic substitution pattern was observed so that participation of a free cationic radical can be ruled out. However, the possibility of an auration reaction, or a Friedel–Crafts type substitution or even the participation of coordinated radical cation are possible pathways to explain these transformation.

Scheme 23. Gold-catalyzed oxidative homocoupling of simple arenes with $PhI(OAc)_2$



Waser and co-workers reported in 2009 a gold-catalyzed alkynylation of indoles, pyrroles and thiophenes using pre-formed alkynyl-iodonium derivatives[74] (Scheme 24).[75] The presence of a halogen atom in the aromatic substrates is tolerated, thus highlighting the orthogonality of the method compared to classical Pd-catalyzed cross-coupling reactions. Two possible catalytic cycles have been proposed for this transformation. The first would involve the formation of a gold(III) acetylene complex **41**, which reacts by aurating the heteroaromatic ring to give an organogold(III) intermediate **42**. The latter evolves by reductive elimination to give the C_3-alkynylated product **43**.

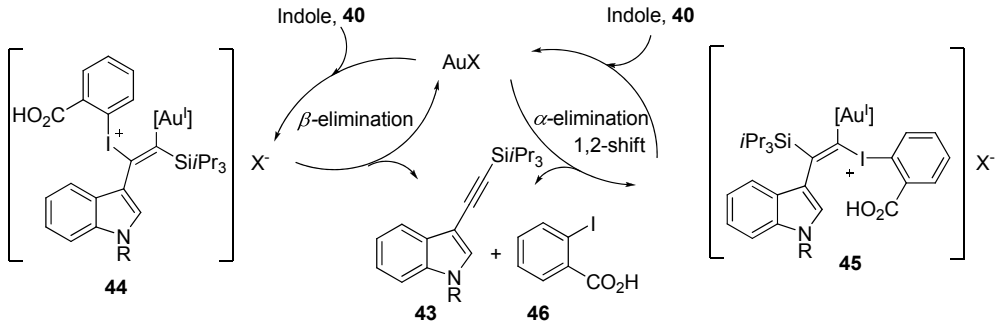
Scheme 24. Gold-catalyzed alkynylation of heteroaromatics



The second pathway would involve first the addition of the indole to the activated triple bond of the hypervalent iodine derivative to form a vinyl-gold intermediate (**44** or regioisomer **45** in Scheme 25). The end of the catalytic cycle comprises a β-elimination or an α-elimination/1,2-shift sequence to give 2-iodobenzoic acid and alkynylated product **43**.

However, experimental evidence does not suffice to distinguish between these two hypotheses.

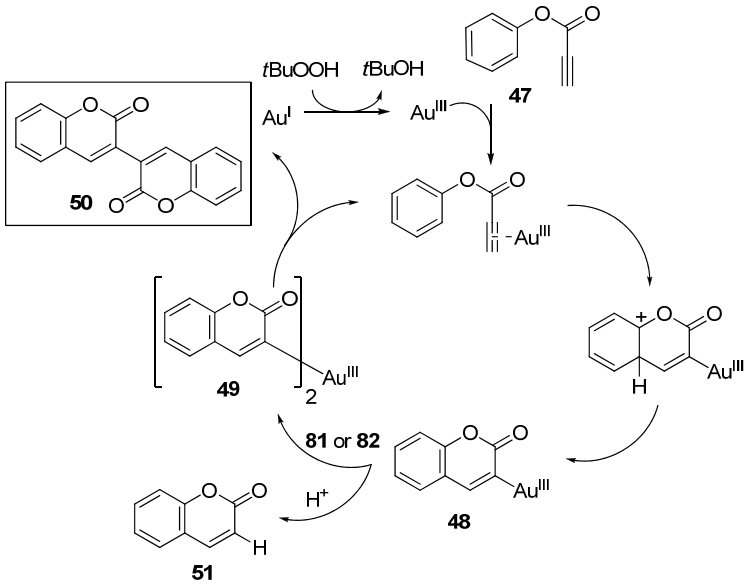
Scheme 25. Plausible mechanism for the oxidative alkynylation on indoles



1.4.4.2 Cascade nucleophilic addition-oxidative coupling reactions

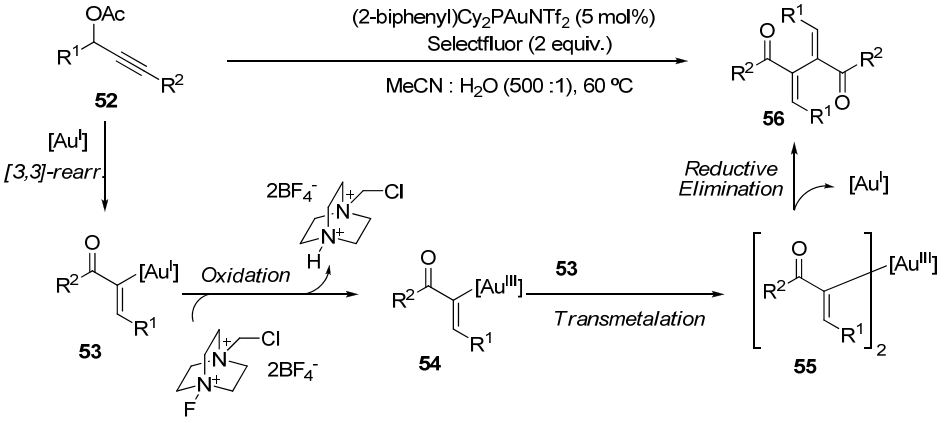
More elaborated homocoupling products can be obtained by combining cyclizations with gold(I)/gold(III) catalytic cycles. Wegner and co-workers reported the gold-catalyzed cyclization of arylpropionic esters (**47**) (Scheme 26).[76] Bis-coumarins (**50**) can be formed in moderate to good yields in the presence of $HAuCl_4$ and *t*BuOOH as oxidant. The reaction, which has also been extended to benzofurans, is proposed to occur through a first cyclization step catalyzed by gold(III) to give **48** after a re-aromatization step. Complex **48** can work as catalyst for another cyclization of **47** or react with itself through a ligand exchange process to give intermediate **49**, which upon reductive elimination delivers the observed homocoupling product **50** and gold(I), which is re-oxidized in the presence of *tert*-butylhydroperoxide. Alternatively, protonolysis of **48** could explain the formation of coumarin **51** as major by-product in this process.

Scheme 26. Cascade cyclization-oxidative dimerization of aryl propargyl acids



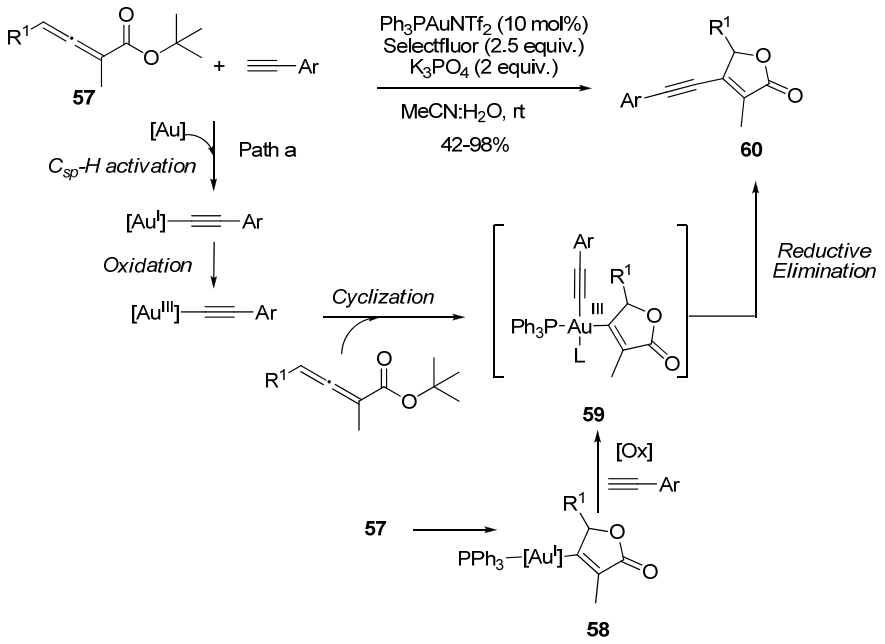
Zhang has developed a highly efficient gold-catalyzed oxidative dimerization of propargylic acetates (**52**) pioneering the use Selectfluor as oxidant (Scheme 27).[77] Gold(I) catalyzed the acyloxy rearrangement to the corresponding vinyl-gold(I)-keto species (**53**), which are oxidized with Selectfluor to gold(III)-complexes (**54**). Upon transmetalation with **53** and reductive elimination on the gold(III) center, dimerization products (**56**) are obtained.

Scheme 27. Cascade Rearrangement-oxidative dimerization of propargyl acetates



Gouverneur has combined allenoates and terminal alkynes in a gold catalyzed cyclization/oxidative alkynylation cascade to give *β*-alkynyl-*δ*-butenolides (**60**) (Scheme 28).[78]

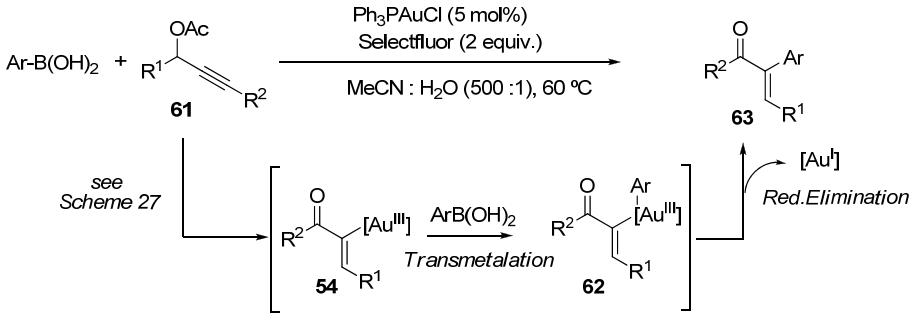
Scheme 28. Gold-catalyzed synthesis of *β*-alkynyl-*δ*-butenolides



Two different mechanistic pathways can be envisioned to explain this transformation. On one hand the reaction could proceed via C-H activation of the terminal alkyne to form gold acetylide followed by oxidation to gold(III) intermediate which undergoes cyclization to form **59**. On the other hand gold(I) could mediate the cyclization of the allenoate followed by oxidation and then reaction with the alkyne or acetylide to give **59**. In both cases gold(I) species, upon oxidation in the presence of a strong oxidant such as Selectfluor, are proposed to deliver the gold(III) intermediate that evolves *via* reductive elimination to form the new Csp^2-Csp bond.

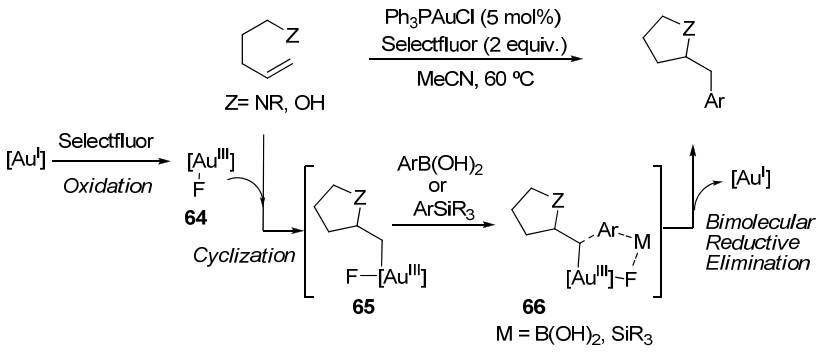
Further inspiration has been drawn from Pd(0)/Pd(II) catalytic cycles, to develop gold catalyzed cross-coupling processes. Zhang and co-workers devised an efficient synthesis of *α*-arylenones through an oxidative cross coupling of propargyl acetates and boronic acids.[79] This transformation takes advantage of the recognized ability of gold to, upon coordination to the triple bond, trigger the migration of the acetoxy group (see Scheme 27). The vinyl-gold(I) intermediate **53** generated in situ is oxidized in the presence of selectfluor to a vinyl-gold(III) intermediate **54**, which undergoes, similarly to Pd(II) intermediates, a transmetalation process in the presence of boronic acids to give intermediate **62**, so that upon reductive elimination a new Csp^2-Csp^2 bond is formed **63** (Scheme 29).

Scheme 29. Cascade rearrangement-oxidative coupling with boronic acids



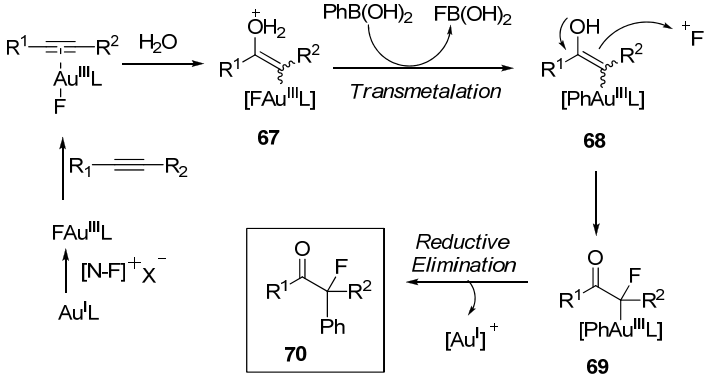
Different synthetic applications of the [gold(I)]/Selectfluor system in the oxidative carbohetero-functionalization of alkenes have been reported by Zhang,[80] Toste[81] and Lloyd-Jones[82] (Scheme 30). In these transformations, activation of the double bond seems to occur via gold(III) species (**64**) which are formed in the first step of the catalytic cycle from the reaction of gold(I) complexes with Selectfluor. Next, the intramolecular attack of a N/O-nucleophile affords an alkyl–gold(III) intermediate **65**, which in the presence of aryl boronic acids or aryl silanes reacts through a bimolecular reductive elimination to give the new Csp^3-Csp^2 bonds. An alternative mechanism would involve a transmetalation event on **64** or **65** to give gold(III)-Ar species prior to the reductive elimination, although experimental evidences seem to disfavor this hypothesis. Intermolecular versions of these reactions have also been simultaneously reported.[82,83]

Scheme 30. Cascade cyclization-oxidative arylation of alkenes



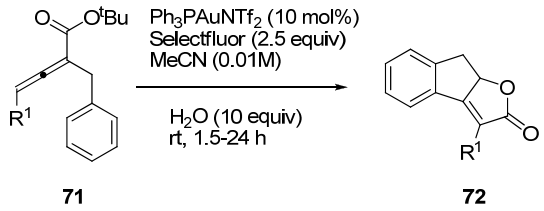
Xu and Hammond reported one-pot tandem addition/oxidative coupling/fluorination reaction using readily available alkynes as starting materials.[84] They propose the initial oxidation of gold(I) to gold(III) in the presence of Selectfluor followed by the attack of water onto gold activated alkyne to generate vinyl-gold species **67.** Upon transmetalation with the phenylboronic acid to form the vinyl-gold complex **68** is formed. This intermediate reacts with Selectfluor to give the gold species **69**, which upon reductive elimination afford the observed α-fluoroketones **70** (Scheme 31).

Scheme 31. One-pot tandem addition/oxidative coupling/fluorination reaction



In all these gold-catalyzed intermolecular cascades involving nucleophilic addition and intermolecular oxidative arylation reactions, the aryl counterpart derives from conventional metalated precursors such as boronic acids or silanes. An elegant approach using simple arenes was reported by Gouverneur in an intramolecular process.[85] In this case, gold mediates both, the activation of carbon-carbon bond and the Csp^2-H functionalization. Benzyl-substituted tert-butyl allenoates **71** underwent 5-endo-dig cyclization followed by intramolecular oxidative arylation with the benzyl group in the presence of catalytic amount of $Ph_3PAuNTf_2$ to form indenofuranones **72** (Scheme 32). A similar gold(I)-catalyzed cascade aminocyclization/intramolecular oxidative arylation of alkenes has been reported by Zhang.[86]

Scheme 32. Cyclization-oxidative arylation of *tert*-butyl allenoates



71 **72**

1.5 Objectives

The direct and selective replacement of carbon-hydrogen bonds with new bonds (such as C-C, C-O, C-N and C-F) represents an important and long-standing goal in chemistry. These transformations have broad potential in synthesis because C-H bonds are ubiquitous in organic compounds. In addition, achieving selectivity among many different C-H bonds remind a challenge. In the last years C-H functionalization catalyzed by transition metals has progressed considerably, highlighting the potential of organometallic chemistry for useful C-H activation processes.

Among the catalysts that allow selective transformations, gold has proven in recent times to be the metal of choice concerning the activation of multiple C-C bonds. One of the most

interesting features is its ability to act as mild, carbophilic π-Lewis acid.[3] π-Bonds activated by gold can undergo the addition of nucleophiles, rearrangement of propargyl carboxylates, or cycloisomerizations among other transformations.[2,3] However, oxidative couplings in which the redox pair gold(I)/gold(III) is responsible of the catalyst, are less frequently disclosed. In fact, before this PhD thesis was started, the oxidation of methane to methanol by gold(I)/gold(III) redox catalytic cycles reported by Periana (section 1.4.1),[69] was the only example in the literature. Nevertheless, in the last four years this field has attracted a lot of attention as is described in the section 1.4.

The work described in this thesis is dedicated to the development of new C-H functionalization reactions based on gold(I)/gold(III) redox catalytic cycles for the construction of new C-C and C-heteroatom bonds to enable a rapid and efficient construction of molecular complexity.

The first chapter of this thesis (Chapter 2) will describe a novel gold catalyzed ethynylation of arenes via C-H functionalization of both organic counterparts, electron rich arenes and electron deficient alkynes, where the redox pair gold(I)/gold(III) is the responsible of the catalyst. A detailed mechanistic study of this transformation will be presented in the Chapter 3.

In the second part of this thesis, cascade reactions based on the combination of the unique reactivity of gold as a carbophilic Lewis acid with oxidative couplings, enabling the construction of C-C, C-O, C-N and C-F bonds will be described. In these tandem reactions, the gold catalyst first delivers the organic fragment by acting in its traditional role as a redox-inert π-acid and then mediates the formation of a new C-C or C-heteroatom bond by oxidative coupling. The Chapter 4 will focus on the development of a gold-catalyzed regioselective difunctionalization of alkenes. Aminooxygenation of unactivated alkenes and a novel aminoamidation by gold activation of nitriles will be presented. In addition, the synthesis of diastereomerically pure tricyclic 3-benzazepines as a result of a gold-catalyzed oxidative arylation reaction will be also described.

Chapter 5 and 6 will describe fluorination reactions catalyzed by gold. An efficient method to synthesize α-fluoroenones based on a tandem gold-catalyzed process starting from easily available propargyl acetates and gold-catalyzed synthesis of α-fluoro acetals and α-fluoro ketones from alkynes using Selectfluor as the stoichiometric source of fluorine will be reported therein.

1.6 References

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Chapter 2

Gold-Catalyzed Ethynylation of Arenes

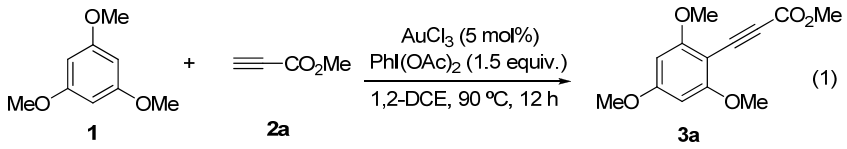
CHAPTER 2

Gold-Catalyzed Ethynylation of Arenes

Teresa de Haro and Cristina Nevado*

(*J. Am. Chem. Soc.* **2010**, *132*, 1512)

The introduction of acetylenic groups in organic molecules is an important synthetic transformation. Among all available methods,[1] Sonogashira cross-coupling reaction is the most widely spread.[2] Due to its versatility, the palladium-catalyzed Csp^2-Csp reaction between aryl halides (particularly iodides) and terminal alkynes, with or without the presence of a copper co-catalyst, efficiently produces aryl-alkynes, which are precursors for bioactive natural molecules, pharmaceuticals and molecular organic materials.[3] Nevertheless, several drawbacks still limit the scope of this ubiquitous transformation: first, alkynes containing electron-withdrawing groups directly attached to the ethynyl carbon poorly react with aryl halides.[4] Second, if the aromatic halide is "deactivated", that is, electron-rich, oxidative addition is more difficult making any cross-coupling reaction extremely challenging.[5] Activation of aromatic C-H bonds followed by C-C bond formation constitutes a conceptually attractive methodology since it avoids the otherwise necessary prefunctionalization of the aromatic counterpart.[6] Described here is the first ethynylation of "deactivated" arenes with electron-deficient alkynes via a gold-catalyzed C-H functionalization of both aromatic and acetylenic counterparts.[7]



The reaction of 1,3,5-trimethoxybenzene (**1**) with methyl propiolate (**2a**) in the presence of $AuCl_3$ (5 mol%) and $PhI(OAc)_2$ (1.5 equiv.) in 1,2-dicloroethane at 90 ºC afforded 3-(2,4,6-trimethoxyphenyl)propiolate (**3a**) in 45% yield (eq. 1). Neither previously described hydroarylation of the alkyne[8] nor homocoupling of the aromatic counterpart was detected in the reaction mixture.[9] This result prompted us to optimize the reaction conditions and study its scope.[10]

We first examined the influence of the gold source on the reaction: cationic gold complexes such as $Ph_3PAuNTf_2$ or $Ph_3PAuOTf$ afforded **3a** in 43 and 70% yield respectively (Table 1,

entries 1-2). Surprisingly, when neutral PPh_3AuCl was used, 72% yield of **3a** was obtained becoming the catalyst of choice for the reaction (entry 3). Other metals such as Pd(II) or Cu(I) did not effect the abovementioned transformation (Table 1, entries 4 and 5). Next, we studied the sensitivity of the reaction to both, solvent polarity and coordinating ability: toluene afforded **3a** in 28% yield whereas polar nitromethane or acetonitrile delivered the product in trace amounts (entry 6). The presence of water totally inhibited the desired reactivity (Table 1, entry 7). Addition of different bases was also examined:[10] MgO and K_2CO_3 showed moderate improvement (entry 8), whereas $NaHCO_3$ afforded **3a** in an optimized 85% yield (entry 9). Finally, the key role of the oxidant was unravelled. PhIO gave **3a** in 55% yield (entry 10) whereas neither selectfluor nor *tert*-butylhydroperoxide, well-known oxidants for gold catalysts,[11] effects any conversion of **1** (Table 1, entries 11,12). Thus, we decided to use conditions from entry 9 to study the reaction scope.

Table 1. Optimization for the Gold-Catalyzed Ethynylation of **1**

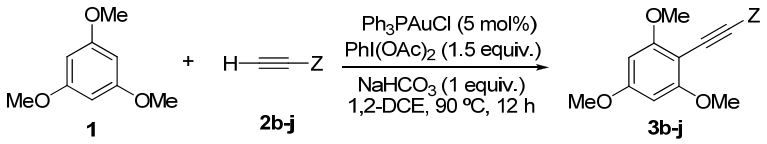
Entry	Reaction Conditions[a]	Yield %[b]
1[c]	$Ph_3PAuNTf_2$ (5 mol%), 1,2-DCE	43
2[c]	$Ph_3PAuOTf$ (5 mol%), 1,2-DCE	70
3[c]	Ph_3PAuCl (5 mol%), 1,2-DCE	72
4[d]	$Pd(OAc)_2$ (5 mol%), 1,2-DCE	-
5[d]	CuI (5 mol%),1,2-DCE	-
6[c]	Ph_3PAuCl (5 mol%), Toluene / CH_3NO_2 /CH_3CN	28/7/6
7[c]	Ph_3PAuCl (5 mol%), 1,2-DCE:H_2O (100:1)	-
8[c]	Ph_3PAuCl (5 mol%), MgO/ K_2CO_3 (1.5 eq.), 1,2-DCE	64/77
9[c]	**Ph_3PauCl (5 mol%), $NaHCO_3$ (1 equiv.), 1,2-DCE**	**85 (81%)**[e]
10	Ph_3PauCl (5 mol%), $NaHCO_3$ (1 equiv.), PhIO	55
11	Ph_3PauCl (5 mol%), $NaHCO_3$ (1 equiv.), Selectfluor	-
12	Ph_3PauCl (5 mol%), $NaHCO_3$ (1 equiv.), or *t*-BuOOH	-

[a] Reaction conditions: **1** (2 equiv.), **2a** (1 equiv.), 0.5 M at 90 ºC in a sealed tube for 12 h. [b] Determined by GC-MS (isolated yield in brackets). [c] $PhI(OAc)_2$ (1.5 equiv.). [d] With and without $PhI(OAc)_2$. [e] 2-Iodo-1,3,5-trimethoxybenzene **4** could be isolated in 20% yield in entries 1-10.[12]

The ethynylation reactions of **1** with various terminal alkynes have been summarized in Table 2. Ethyl and *tert*-butyl propiolates **2b-c** showed a comparable reactivity to **2a** (Table 2, entries 1-2). Aromatic as well as aliphatic acetylenic ketones (**2d-h)** could also be efficiently coupled with this method to give arylated products **3d-h** in moderate to good yields (entries 3-7). The

reaction of **1** with methyl enyne **2i** afforded aryl-substituted enyne **3i** in 48% yield (entry 8). Finally, phenyl acetylene **2j** produced the expected ethynylated product (**3j**) in low yield due to homocoupling of the alkyne (entry 9).

Table 2. Scope of Gold-Catalyzed Ethynylation of **1**[a]

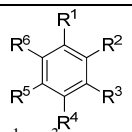
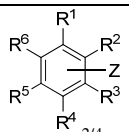
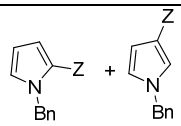
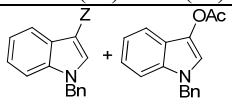
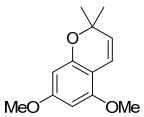
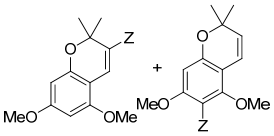


Entry[a]	Substrate	Product (yield %)[b]
1	**2b**, Z = CO_2Et	**3b** (75)
2	**2c**, Z = CO_2tBu	**3c** (60)
3	**2d**, Z = COPh	**3d** (72)
4	**2e**,Z=CO(3,5-dimethoxy-phenyl)	**3e** (68)
5	**2f**, Z = CO(*p*-$CF_3C_6H_4$)	**3f** (70)
6	**2g**, Z = CO*t*Bu	**3g** (31) [c]
7	**2h**, Z = CO(C_7H_{12})	**3h** (66)
8	**2i**, Z = $(CH_3)C{=}CH_2$	**3i** (48)
9	**2j**, Z = Ph	**3j** (25)

[a] Reactions carried out with **1** (2 equiv.), **2b-j** (1 equiv.), 0.5 M in a sealed tube. [b] Isolated yield after column chromatography. [c] Microwave reactor: 62% yield based on recovered starting material (**1**).

We have extended this reaction to other electron-rich aromatic rings. The presence of groups such as benzyl, *iso*-propyl and methoxymethyl (MOM) ethers (**5a-d**) was well tolerated affording the corresponding ethynylation products **6a-d** as regiomeric mixtures in good yields. Substrates such as **5e-h** were transformed into single regioisomers **6e-h** in moderate yields, revealing that *para/ortho*- is preferred over *ortho/ortho*-activation in the arene. The presence of inductive donating groups such in **5i-k** was also well accommodated although mesomeric activation seemed to be preferred. Heteroaromatic rings are also suitable substrates for this reaction:[13] *N*-benzyl pyrrol (**7**) delivered ethynylated regioisomers **8a** and **8b** in 43 and 26% yield respectively. *N*-benzyl indole **9** afforded **10a** in 60% yield together with acetoxy derivative **10b**. Finally, conjugated system **11** produced the cross-coupling products both in the chromene (**12a**) and aromatic ring (**12b**) in 48 and 22% yield respectively. In all cases, no hydroarylation products could be detected in the reaction mixtures.

Table 3. Scope of Au-Catalyzed Ethynylation of Arenes[a]

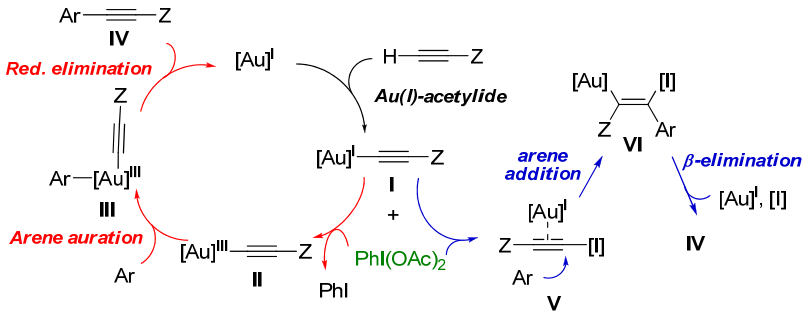
Substrate[b]	Product, yield(%)[c]	Substrate[b]	Product (yield %)[c]
			
5a: R^1=R^3=OMe, R^5=OBn	**6a+6a´** ($R^{2/4}$ = Z), 75[d]	**7**	**8a** (43) **8b** (26)
5b: R^1=R^3=OMe, R^5=O*i*Pr	**6b+6b´** ($R^{2/4}$ = Z), 62[d]		
5c: R^1=R^3=OMe,R^5=OMOM	**6c+6c´** ($R^{2/4}$ = Z), 75[d]	**9**[e]	**10a** (60) **10b** (12)
5d: R^1= R^3=R^5=OBn,	**6d** (R^2 = Z), 42		
5e: R^1=R^2=R^4=OMe	**6e** (R^5 = Z), 56		
5f: R^1=R^2=R^3=OMe	**6f** (R^4 = Z), 25	**11**	**12a** (48) **12b** (22)
5g: R^1=R^3=OMe	**6g** (R^4 = Z), 52		
5h: R^3=OMe, R^5=R^6=-OCH_2O-	**6h** (R^2 = Z), 40		
5i: R^1=R^3= OMe, R^5=Me	**6i** (R^4 = Z), 70		
5j: R^1=R^3=R^5=OMe, R^2=Me	**6j** (R^4 = Z), 60		
5k: R^1=R^2=R^6=OMe, R^4=Me	**6k** (R^3 = Z), 51		

[a] Reaction conditions: arene (2 equiv.), **2a** (1 equiv.), Ph_3PAuCl (5 mol%), $PhI(OAc)_2$ (1.5 equiv.) in 1,2-DCE (0.5 M) at 90ºC in a sealed tube. [b] Undefined substituents: R^x=H; Z = -C≡C(CO_2Me). [c] Isolated yield after column chromatography. [d] Ratio 2:1. [e] $PhI(OAc)_2$ (1 equiv.), pre-heated oil bath.

NMR experiments were conducted to elucidate the reaction mechanism. ^{31}P-NMR analysis of the reaction of **2a** with a stoichiometric amount of Ph_3PAuCl in CD_2Cl_2 showed a sharp peak at 34.2 ppm, which corresponds to the pure complex. Upon heating to 90 ºC, a new signal at 42.3 ppm was observed. This peak is attributed to the formation of gold(I)-acetylide **I** (see Scheme 1, Z = CO_2Me) by comparison with a pure sample of this complex synthesized independently.[14] Interestingly, in the catalytic reaction of compound **5i** with **2a**, the formation of complex **I** could also be detected by ^{1}H and ^{31}P NMR.[10]

With these results in hand, two possible reaction pathways can be envisioned starting with the formation of gold(I)-acetylide complex (**I**). In the presence of $PhI(OAc)_2$, **I** can be oxidized to a gold(III)-alkynyl intermediate (**II**).[15] The reaction of the arene with complex **II** might occur via electrophilic aromatic substitution or Csp^2-H activation process to give aryl-aurate species **III**. Finally, upon reductive elimination, the new Csp^2-Csp bond is formed and the alkynylated products (**IV**) are obtained (Scheme 1, red path). Alternatively, the reaction of **I** with $PhI(OAc)_2$ could afford an electrophilic alkynyl-iodonium complex (**V**). A gold-mediated addition of the aromatic ring to the triple bond in **V** affords a vinyl gold intermediate **VI**, which upon *β*-elimination would deliver the arylated alkynes **IV** (Scheme 1, blue path).[13]

Scheme 1. Mechanistic Proposal for the Au-Catalyzed Ethynylation of Arenes



In summary, we report here the first gold-catalyzed ethynylation of arenes with electron-deficient alkynes via gold catalyzed C-H activation of both Csp and Csp^2-H bonds. This transformation provides aromatic propiolates difficult to prepare by other methods. Further studies to expand the reaction scope and get a deeper insight into the reaction mechanism are currently underway and will be reported in due course.

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[10] Further studies can be found in Chapter II: Experimental section

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[12] Reaction of **4** with **2a** under the optimized conditions from Table 1 did not afford compound **3a**, ruling out a gold-catalyzed Sonogashira-reaction mechanism as in: González-Arellano, C.; Abad, A.; Corma, A.; García, H.; Iglesias, M.; Sánchez, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1536. (See Supplementary data).

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Chapter 2

Experimental Section

Table of Contents

2. 1 General information

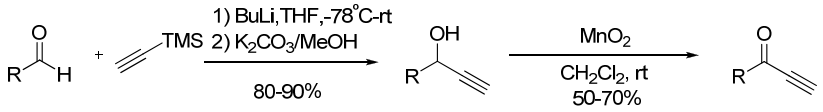
NMR spectra were recorded on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual ^{1}H and ^{13}C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution electrospray ionization mass spectrometry was performed on a Finnigan MAT 900 (Thermo Finnigan, San Jose, CA; USA) doublefocusing magnetic sector mass spectrometer. Ten spectra were acquired. A mass accuracy ≤ 2 ppm was obtained in the peak matching acquisition mode by using a solution containing 2 µl PEG200, 2 µl PPG450, and 1.5 mg NaOAc (all obtained from Sigma-Aldrich, CH-Buchs) dissolved in 100ml MeOH (HPLC Supra grade, Scharlau, E-Barcelona) as internal standard. GC-MS analysis was done on a Finnigan Voyager GC8000 Top. GS analysis for the screening of the reaction was done on a Trace GS 2000 series. The Column employed is a Zebron Phase: ZB-5, 30m x 0.25mm x df = 0.25µl. The Method employed was 5 minutes at 40 °C then 10 minutes at 250 °C with an over-run time of 29 minutes. Dodecane was used as an internal standard. Microwave reactions for the preparation of compounds **3g** was carried out in microwave synthesis systems which were built upon CEM's Focused™ Microwave Technology at 150 watts and 90 °C for 40 minutes.

Materials and Methods: Unless otherwise stated, starting materials were purchased from Aldrich and/or Fluka. All reagents were used as received except for iodobenzene diacetate, which was recrystallized from an aqueous solution of acetic acid (5 M) and dried overnight under high vacuum.[1] Potassium carbonate and sodium bicarbonate was dried overnight at 80 ^{0}C. PPh_3AuCl was prepared according to previously reported procedures.[2] Solvents were purchased in HPLC quality, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Unless otherwise stated, reactions WERE NOT run under inert atmosphere. Conversion was monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. Flash column chromatography was performed over silica gel (230-400 mesh).

2.2 Preparation and characterization of starting materials

2.2.1 General procedure for the preparation of propargylic ketones

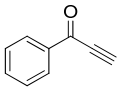
Scheme 1. Synthesis of propargyl ketones



To a solution of trimethylsilyl acetylene (1.1 equiv.) in THF at -78 °C under N_2 atmosphere, *n*-BuLi (1.05 equiv., 1.6 M in hexane) was added dropwise. The mixture was stirred for 1 h at -78 °C, the corresponding aldehyde (1 equiv.) was then added and the reaction was stirred for additional 30 min at -78 °C and warmed up to room temperature in 30 min. Then, the mixture was quenched with water and extracted with diethyl ether. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. K_2CO_3 (3 equiv.) was added to the crude mixture in MeOH and stirring was continued at room temperature for 2 h. The crude was filtered under a pad of Celite and washed with dichloromethane. The residue was washed with ammonium chloride and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to afford the corresponding propargylic alcohol in 80-90% yield. The crude alcohol was dissolved in dichloromethane and treated with MnO_2 (15 equiv.). After stirring at room temperature for 2 h, the reaction was complete as determined by TLC. Excess MnO_2 was removed by filtration of the reaction mixture through a pad of Celite. The filtrate was washed sequentially with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford a yellow residue that was purified by flash column chromatography. The desired propargylic ketones were obtained in 50-70% yield.

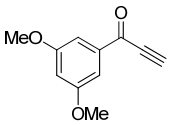
2.2.2 Characterization of propargyl ketones

1-Phenyl-2-propyn-1-one (2d)[3]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17-8.15 (m, 2H), 7.65-7.61 (m, 1H), 7.52- 7.47 (m, 2H), 3.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 136.7, 135.0, 130.2, 129.2, 81.2, 80.8.

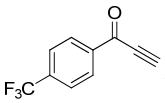
1-(3,5-Trimethoxyphenyl)-2-propyn-1-one (2e)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, J = 2.5 Hz, 2H), 6.69 (t, J = 2.5 Hz, 1H), 3.83 (s, 6H), 3.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 161.4, 138.5, 107.8,

107.7, 81.1, 80.8, 56.6. IR (film): $\tilde{\upsilon}$ = 3255, 2942, 2840, 2096, 1649, 1590, 1457, 1427, 1321, 1301, 1205, 1157, 1063, 1029, 747 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{10}H_{11}O_3$: 191.0702, found: 191.0700.

1-(*p*-Trifluorophenyl)-2-propyn-1-one (2f)[4]

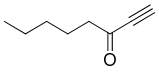


^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 3.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 139.1, 136.1 (q, *J* = 33 Hz), 130.5, 126.4 (q, *J* = 3.8 Hz), 82.5, 80.3.

4,4-Dimethyl-1-pentyn-3-one (2g)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.23 (s, 1H), 1.15 (s , 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.4, 80.1, 79.5, 44.6, 25.6.

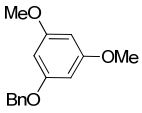
1-Octyn-3-one (2h)[5]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (s, 1H), 2.57 (t , *J* = 7.5 Hz, 2H), 1.67 (quint, *J* = 7.5 Hz, 2H), 1.33-1.27 (m, 4H), 0.89 (t, *J* = 6.7 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.6, 81.5, 78.2, 45.4, 31.0, 23.4, 22.3, 13.8.

2.2.3 Preparation of aromatic substrates

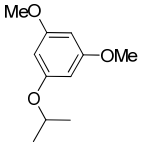
1-Benzyl-3,5-dimethoxy-benzene (5a)



Compound **5a** was prepared from 3,5-dimethoxyphenol (309 mg, 2.0 mmol), potassium carbonate (552 mg, 4.0 mmol) and benzyl chloride (0.28 mL, 2.4 mmol) in DMF (8 mL). The mixture was stirred for 17 h, quenched with ammonium chloride saturated solution and extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with water (3 x 10 mL), aqueous sodium hydroxide (2M, 10 mL) and brine, dried over $MgSO_4$ and evaporated under reduced pressure to give the compound as colorless oil (200 mg, 1.2 mmol) in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43-7.30 (m, 5H), 6.16 (d, *J* = 2.2 Hz, 2H), 6.10 (t, *J* = 2.2 Hz, 1H), 5.02 (s, 2H), 3.76 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 161.2, 137.4, 129.1, 128.5, 128.1, 94.2, 93.7, 70.6, 55.8.

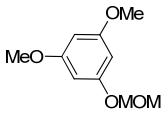
2.2.4 Characterization of aromatic substrates

3,5-Dimethoxypheny-1-*i*sopropyl ether (5b)[6]



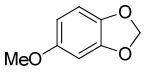
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08-6.06 (m, 3H), 4.50 (sept, J = 6.0 Hz, 1H), 3.76 (s, 6H), 1.33 (d, J = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 160.3, 95.1, 93.3, 70.4, 55.8, 22.6.

3,5-Dimethoxyphenyl-1-methoxymethylether (5c)[7]



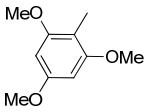
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.23 (d, J = 2.2 Hz, 2H), 6.14 (t, J = 2.2 Hz, 1H), 5.14 (s, 2H), 3.66 (s, 6H) 3.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 159.4, 95.2, 94.7, 94.5, 56.3, 55.6.

4-Methoxybenzo[1,3]dioxole (5h)[8]



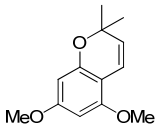
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (d, J = 8.6 Hz, 1H), 6.49 (d, J = 2.6 Hz, 1H), 6.31 (dd, J = 8.6, 2.6 Hz, 1H), 5.90 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 148.8, 142.1, 108.4, 105.2, 101.6, 98.0, 56.5.

1,3,5-Trimethoxy-2-methylbenzene (5j)[9]



^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.14 (s, 2H), 3.80 (s, 9H), 2.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 159,1, 107.1, 90.8, 55.9, 55.6, 7.9.

5,7-Dimethoxy-2,2-dimethyl-2H-chromene (11)[10]



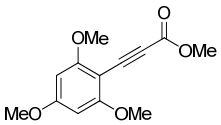
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (d, J = 9.9 Hz, 1H), 6.03 (d, J = 2.1 Hz, 1H), 6.01 (d, J = 2.1 Hz, 1H), 5.41 (d, J = 9.9 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 1.41 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 156.7, 155.2, 126.4, 117.2, 104.7, 94.5, 92.0, 76.7, 56.0, 55.8, 28.3.

2.3 General procedure for gold-catalyzed ethynylation reaction

To a solution of the arene (2 equiv.), iodobenzene diacetate (1.5 equiv.), $NaHCO_3$ (1.05 equiv.) and the corresponding alkyne (1 equiv.) in anhydrous 1,2-dichloroethane (0.5 M) was added PPh_3AuCl (0.05 equiv.) The reaction was stirred at 90 °C for 12 h without inert atmosphere. The crude was filtered under a pad of Celite and purified by flash column chromatography on silica gel.

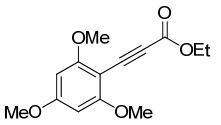
2.4 Characterization of products

Methyl-3-(2,4,6-trimethoxyphenyl)-propiolate (3a)



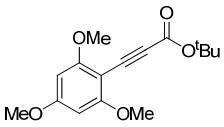
Following the general procedure, compound **3a** was isolated in 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 164.0, 155.0, 91.1, 90.4, 87.5, 81.7, 56.1, 55.5, 52.4. IR (film): $\tilde{\upsilon}$ = 2952, 2921, 2843, 2199, 2009, 1697, 1568, 1472, 1437, 1410, 1344, 1290, 1224, 1209, 1153, 1124, 808, 745, 640 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{13}H_{14}NaO_5$: 273.0733, found: 273.0730.

Ethyl-3-(2,4,6-trimethoxyphenyl)-propiolate (3b)



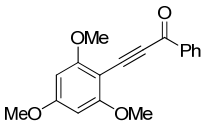
Following the general procedure, compound **3b** was isolated in 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06 (s, 2H), 4.26 (q, *J* = 7.3 Hz, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 1.33 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 164.4, 155.1, 91.6, 90.8, 88.7, 81.6, 62.2, 56.6, 56.0, 14.7. IR (film): $\tilde{\upsilon}$ = 2975, 2941, 2845, 2192, 1692, 1603, 1572, 1496, 1474, 1412, 1365, 1344, 1291, 1226, 1209, 1178, 1127, 808, 746 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{16}NaO_5$: 287.0889, found: 287.0891.

***t*-Butyl-3-(2,4,6-trimethoxyphenyl)-propiolate (3c)**



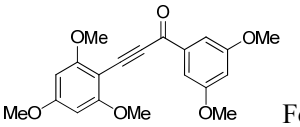
Following the general procedure, compound **3c** was isolated in 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.04 (s, 2H), 3.85 (s, 6H), 3.82 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 164.1, 154.2, 91.9, 90.8, 90.1, 83.2, 79.0, 56.6, 56.0, 28.6. IR (film): $\tilde{\upsilon}$ = 2977, 2937, 2854, 2195, 1694, 1601, 1575, 1497, 1470, 1369, 1294, 1229, 1207, 1144, 1130, 955, 730 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{16}H_{20}NaO_5$: 315.1202, found: 315.1205.

3-(2,4,6-Trimethoxyphenyl)-1-phenyl-2-propyn-1-one (3d)



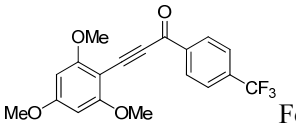
Following the general procedure, compound **3d** was isolated in 72% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.35 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 6.10 (s, 2H), 3.92 (s, 6H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ =178.6, 165.2, 165.0, 138.2, 133.9, 130.3, 128.9, 96.4, 92.5, 91.1, 90.0, 56.7, 56.2. IR (film): $\tilde{\upsilon}$ = 2942, 2843, 2178, 1630, 1598, 1575, 1471, 1345, 1293, 1230, 1208, 1175, 1159, 1132, 733, 701 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{18}H_{16}NaO_4$: 319.0940, found: 319.0940.

3-(2,4,6-Trimethoxyphenyl)-1-(3,5-dimethoxyphenyl)- 2-propyn-1-one (3e)



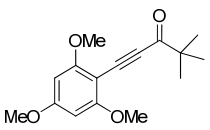
Following the general procedure, compound **3e** was isolated in 68% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 2.3 Hz, 2H), 6.67 (t, J = 2.3 Hz, 1H), 6.10 (s, 2H), 3.93 (s, 6H), 3.87 (s, 3H), 3.86 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =177.8, 164.7, 164.5, 160.7, 139.6, 107.6, 106.0, 96.1, 92.2, 90.4, 89.4, 56.0, 55.6, 55.6. IR (film): $\tilde{\upsilon}$ = 3190, 2942, 2843, 2174, 2153, 1567, 1456, 1426, 1342, 1297, 1231, 1206, 1153, 1124, 1066, 1029, 843, 823, 743 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{20}H_{20}NaO_6$: 379.1152, found: 379.1153.

3-(2,4,6-Trimethoxyphenyl)-1-(*p*-trifluoromethyphenyl)- 2-propyn-1-one (3f)



Following the general procedure, compound **3f** was isolated in 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, J = 8.5 Hz, 2H), 7.75 (t, J = 8.5 Hz, 2H), 6.11 (s, 2H), 3.94 (s, 6H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 165.4, 165.3, 140.7, 135 (q, J = 30 Hz), 130.5, 125.8 (q, J= 3.5 Hz), 122.9, 96.3, 92.0, 91.8, 91.9, 56.6, 56.1. IR (film): $\tilde{\upsilon}$ = 3004, 2942, 2848, 2176, 1633, 1592, 1575, 1455, 1412, 1345, 1324, 1294, 1207, 1129, 1065, 1028, 855, 824, 761 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{19}F_3H_{15}NaO_4$: 387.0814, found: 387.0811.

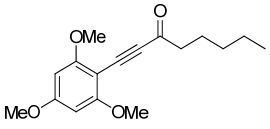
3-(2,4,6-Trimethoxyphenyl)-1-*t*-butyl-2-propyn-1-one (3g)



Compound **3g** was obtained by the following procedure: to a solution of 1,3,5- trimethoxybenzene **1** (42.0 mg, 0.25 mmol), iodobenzene diacetate (60 mg, 0.19

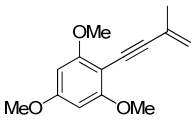
mmol), MgO (5.25 mg, 0.13 mmol,) and 4,4-dimethyl-1-pentyn-3-one (14 μL, 0.125 mmol) in anhydrous 1,2-dichloroethane (0.9 mL) was added PPh_3AuCl (3.0 mg, 0.006 mmol). The reaction was carried out in the Microwave reactor at 150 W and 90 °C for 40 min. Then, the crude was filtered under a pad of celite and purified by flash column chromatography on silica gel in Hexane: AcOEt (10:1) to get the **3g** (10.0 mg, 0.033 mmol) in 31% of yield (62% yield based on recovered starting material **1**); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=194.5, 164.3, 164.0, 94.7, 92.9, 90.2, 88.0, 56.0, 55.5, 44.8, 26.4. IR (film): $\tilde{\upsilon}$ = 2973, 2843, 2181, 1648, 1601, 1576, 1497, 1344, 1292, 1229, 1207, 1159, 1132, 1076, 908, 730 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{16}H_{20}NaO_4$: 299.1253, found: 299.1257.

1-(2,4,6-Trimethoxyphenyl)-1-octyn-3-one (3h)



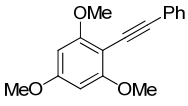
Following the general procedure, compound **3h** was isolated in 66% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 2.62 (t, J = 7.9 Hz, 2H), 1.82-1.75 (m, 2H), 1.36-1.33 (m, 4H), 0.92-0.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.1, 164.7, 164.7, 96.9, 92.1, 90.9, 87.2, 56.5, 56.0, 45.9, 31.8, 24.7, 22.9, 14.4. IR (film): $\tilde{\upsilon}$ = 3003, 2952, 2869, 2181, 1651, 1597, 1573, 1456, 1415, 1342, 1315, 1275, 1231, 1205, 1156, 1129, 1077, 1031, 822, 749 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{17}H_{22}NaO_4$: 313.1410, found: 313.1413.

1-(2,4,6-Trimethoxyphenyl)- 3-buten-1-yne (3i)



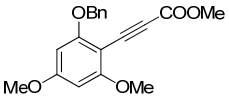
The compound **3i** was obtained by the following modification of the general procedure: To a solution of 1,3,5-trimethoxybenzene **1** (42.0 mg, 0.25 mmol), iodobenzene diacetate (40.0 mg, 0.125 mmol,), $NaHCO_3$ (11.0 mg, 0.13 mmol,) and 2-methyl-1-buten-3-yne (38 μL, 0.41 mmol,) in anhydrous 1,2-dichloroethane (0.9 mL) was added PPh_3AuCl (3.0 mg, 0.006 mmol). The reaction was stirred at 90 ºC for 12 hours. Then, the crude was filtered under a pad of celite and purified by flash column chromatography on silica gel in Hexane: AcOEt (20:1 to 10:1) to get **3i** (20 mg, 0.053 mmol) in 48% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.09 (s, 2H), 5.39-5.37 (m, 1H), 5.24-5.22 (m, 1H), 3.86 (s, 6H), 3.82 (s, 3H), 2.02-2.01 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7, 162.0, 127.9, 121.2, 98.2, 91.0, 81.4, 77.7, 56.6, 55.9, 24.2. IR (film): $\tilde{\upsilon}$ = 3062, 2940, 2840, 1599, 1577, 1578, 1497, 1469, 1436, 1415, 1341, 1309, 1228, 1206, 1156, 1130, 1058, 1036, 908, 731, cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{16}NaO_3$: 255.0991, found: 255.0989.

1-(2-(2,4,6-Trimethoxyphenyl) ethynyl)-benzene (3j)

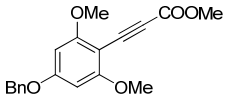


Following the general procedure, compound **3j** was isolated in 25% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57-7.54 (m, 2H), 7.33-7.26 (m, 3H), 6.12 (s, 2H), 3.89 (s, 6H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7, 162.1, 132.0, 128.6, 128.0, 124.8, 96.9, 95.1, 91.1, 82.5, 56.6, 55.9. IR (film): $\tilde{\upsilon}$ = 3062, 3004, 2932, 2843, 2208, 1605, 1592, 1578, 1468, 1415, 1341, 1265, 1227, 1205, 1159, 1126, 1055, 1033, 812, 755, 693 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{17}H_{16}NaO_3$: 291.0991, found: 291.0990.

Methyl-3-(2-Benzyl-4,6-dimethoxy-phenyl)-propiolate (6a) and methyl-3-(4-benzyl-2,6-dimethoxyphenyl)-propiolate (6a')



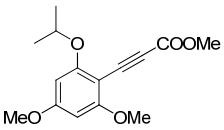
6a



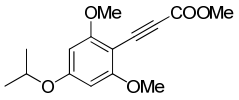
6a'

Following the general procedure, compounds **6a** and **6a'** were isolated as a mixture 2:1 in 75% overall yield; ^{1}H NMR (400 MHz, $CDCl_3$): Major isomer (**6a**): δ = 7.50-7.48 (m, 2H), 7.40-7.29 (m, 3H), 6.10 (d, *J* = 2.3 Hz, 1H), 6.07 (d, J = 2.3 Hz, 1H), 5.17 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H). Minor isomer (**6a'**): δ = 7.50-7.48 (m, 2H), 7.42-7.30 (m, 3H), 6.15 (s, 2H), 5.09 (s, 2H), 3.85 (s, 6H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) of the mixture: δ = 164.3, 164.2, 163.8, 163.5, 163.0, 155.1, 155.0, 136.4, 136.0, 128.8, 128.6, 128.4, 127.8, 127.6, 126.7, 92.2, 91.9, 91.2, 91.2, 90.8, 88.0, 87.9, 81.8, 81.6, 70.5, 70.4, 56.1, 56.1, 55.5, 52.5, 52.5. IR (film): $\tilde{\upsilon}$ = 3004, 2949, 2854, 2204, 1698, 1600, 1574, 1497, 1467, 1455, 1430, 1382, 1288, 1228, 1198, 1153, 1127, 1055, 812, 744, 697 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{19}H_{18}NaO_5$: 349.1046, found: 349.1047.

Methyl-3-(4,6-dimethoxy-2-(*i*-propylether)-phenyl)-propiolate (6b) and methyl-3-(2,6-dimethoxy-4-(*i*-propylether)-phenyl)-propiolate (6b')



6b

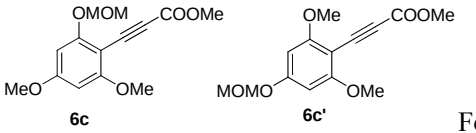


6b'

Following the general procedure, compounds **6b** and **6b'** were isolated as a mixture 1.7:1 respectively in 62% overall yield; ^{1}H NMR (400 MHz, $CDCl_3$) of the mixture: δ = 6.07 (d, *J* = 2.3 Hz, 1H), 6.05 (d, *J* = 2.3 Hz, 1H), 6.04 (s, 0.9H), 4.63-4.50 (m, 1.5H), 3.85 (s, 3H), 3.84 (s, 2.3H), 3.81 (s, 3H), 3.80 (s, 3.9H), 1.37 (d, *J* = 6.0 Hz, 6H), 1.35 (d, *J* = 6.0 Hz, 2.8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 164.8, 164.2,

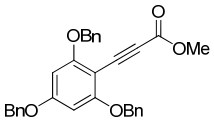
163.7, 162.9, 155.7, 155.6, 94.0, 93.4, 92.3, 91.2, 91.1, 88.2, 88.2, 82.6, 82.4, 72.8, 70.9, 56.5, 56.5, 56.0, 52.9, 22.5, 22.5. IR (film): $\tilde{\upsilon}$ = 2977, 2946, 2844, 2203, 1698, 1599, 1571, 1494, 1466, 1431, 1384, 1287, 1228, 1197, 1170, 1153, 1121, 1056, 908, 814, 730 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{15}H_{18}NaO_5$: 301.1046, found: 301.1045.

Methyl-3-(4,6-dimethoxy-2-(methoxymethylether)-phenyl)-propiolate (6c) and methyl-3-(2,6-dimethoxy-4-(methoxymethylether)-phenyl)-propiolate (6c')



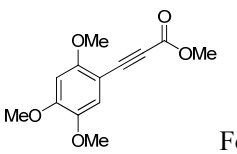
Following the general procedure, compounds **6c** and **6c'** were isolated as a mixture 2:1 respectively in 75% overall yield; ^{1}H NMR (400 MHz, $CDCl_3$) of the mixture: δ = 6.33 (d, *J* = 2.6 Hz, 1H), 6.21 (s, 0.7H), 6.11 (s, d, *J* = 2.6 Hz, 1H), 5.23 (s, 2H), 5.19 (s, 0.9H), 3.86 (s, 3H), 3.85 (s, 2H), 3.81 (s, 3H), 3.81 (s, 3H), 3.80 (s, 0.8H), 3.51 (s, 3H), 3.48 (s, 0.9H) ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 164.0, 163.8, 162.2, 161.7, 155.0, 155.0, 95.0, 94.4, 93.5, 92.5, 92.2, 92.0, 87.9, 87.6, 81.5, 81.4, 56.5, 56.3, 56.1, 56.1, 55.6, 52.5. IR (film): $\tilde{\upsilon}$ = 3010, 2952, 2832, 2206, 1702, 1602, 1575, 1496, 1468, 1433, 1340, 1288, 1230, 1198, 1173, 1152, 1119, 1073, 910, 816, 729 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{16}NaO_6$: 303.0839, found: 303.0837.

Methyl-3-(2,4,6-tribenzylphenyl)-propiolate (6d)



Following the general procedure, compound **6d** was isolated in 42% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.31 (m, 15H), 6.18 (s, 2H), 5.14 (s, 4H), 4.97 (s, 2H), 3.82 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 162.7, 155.1, 136.4, 135.9, 128.7, 128.6, 128.3, 127.8, 127.6, 126.7, 93.5, 88.2, 81.7, 70.5, 70.4, 52.5. (One signal overlapping). IR (film): $\tilde{\upsilon}$ = 3032, 2951, 2921, 2253, 2207, 2167, 1701, 1600, 1574, 1497, 1436, 1375, 1287, 1198, 1155, 1123, 906, 727, 695 cm^{-1}.

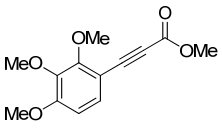
Methyl-3-(2,4,5-trimethoxyphenyl)-propiolate (6e)



Following the general procedure, compound **6e** was isolated in 56% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (s, 1H), 6.47 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =157.9, 154.8, 152.8, 142.9, 116.6, 99.1, 96.6, 84.7, 83.8, 56.6, 56.4, 56.1, 52.6. IR (film): $\tilde{\upsilon}$ = 2989, 2942, 2832, 2203, 1701, 1614,

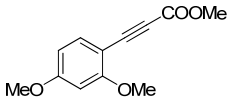
1509, 1456, 1437, 1400, 1353, 1251, 1221, 1132, 1024, 884, 743 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{13}H_{14}NaO_5$: 273.0733, found: 273.0732.

Methyl-3-(2,3,4-trimethoxyphenyl)-propiolate (6f)



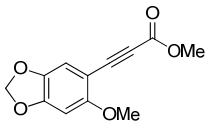
Following the general procedure, compound **6f** was isolated in 25% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.7 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 4.01 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 156.5, 154.7, 142.0, 130.0, 107.4, 106.4, 83.8, 83.4, 61.6, 61.1, 56.2, 52.6. IR (film): $\tilde{\upsilon}$ = 2945, 2843, 2210, 1708, 1591, 1493, 1469, 1437, 1414, 1292, 1220, 1202, 1100, 1057, 908, 804, 730 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{13}H_{14}NaO_5$: 273.0730, found: 273.0733.

Methyl-3-(2,4-dimethoxyphenyl)-propiolate (6g)[11]



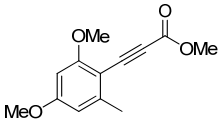
Following the general procedure, compound **6g** was isolated in 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.6 Hz, 1H), 6.47 (dd, J = 8.7, 2.3 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 163.2, 154.9, 136.3, 105.4, 101.2, 98.3, 84.6, 83.7, 55.9, 55.6, 52.6.

Methyl 3-(6-methoxybenzo[d][1,3]dioxol-5-yl)propiolate (6h)



Following the general procedure, compound **6h** was isolated in 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1H), 6.49, (s, 1H), 6.97 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =159.5, 154.8, 151.4, 141.0, 112.8, 102.0, 100.0, 94.4, 84.5, 83.7, 56.7, 52.6. IR (film): $\tilde{\upsilon}$ = 2953, 2900, 2208, 1703, 1617, 1505, 1485, 1455, 1425, 1373, 1284, 1251, 1198, 1156, 1093, 838, 730 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{12}H_{10}O_5Na$: 257.0420, found: 257.0420.

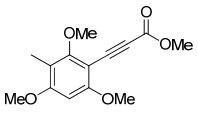
Methyl-3-(6-methyl-2,4-dimethoxyphenyl)-propiolate (6i)



Following the general procedure, compound **6i** was isolated in 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (d, *J* = 1.5 Hz, 1H), 6.27 (d, *J* = 1.5 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 6H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =164.1, 163.0, 155.5, 146.5, 107.3, 101.9, 96.2, 88.2, 84.0, 56.4, 55.9, 53.0, 21.5. IR (film): $\tilde{\upsilon}$ = 3010, 2950, 2843, 2203,

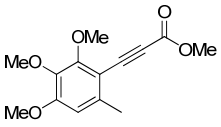
1699, 1600, 1572, 1488, 1458, 1432, 1335, 1282, 1234, 1200, 1132, 1092, 832, 742 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{13}H_{14}NaO_4$: 257.078, found: 257.0785.

Methyl-3-(3-methyl-2,4,6-trimethoxyphenyl)-propiolate (6j)



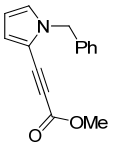
Following the general procedure, compound **6j** was isolated in 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.19 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =162.7, 162.2, 161.7, 155.0, 112.4, 95.3, 90.5, 87.7, 81.8, 61.3, 56.1, 55.7, 52.5, 8.2. IR (film): $\tilde{\upsilon}$ = 2947, 2840, 2205, 1701, 1598, 1573, 1461, 1435, 1401, 1338, 1288, 1209, 1197, 1133, 1117, 807, 746 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{16}NaO_5$: 287.0889, found: 287.0892.

Methyl 3-(2,3,4-trimethoxy-6-methylphenyl)propiolate (6k)



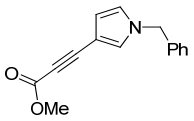
Following the general procedure, compound **6k** was isolated in 51% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.52 (s, 1H), 3.99 (s, 3H), 3.87 (s, 3H), 3.83 (s, 6H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =156.9, 156.2, 155.3, 140.3, 140.0, 109.2, 107.1, 87.7, 83.2, 62.1, 61.6, 56.5, 53.1, 21.2. IR (film): $\tilde{\upsilon}$ = 2941, 2843, 2209, 1706, 1593, 1563, 1494, 1464, 1435, 1403, 1341, 1286, 1238, 1212, 1195, 1129, 1087, 834, 747 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{16}O_5Na$: 287.0889, found: 287.0887.

Methyl 3-(1-benzyl-1H-pyrrol-2-yl)propiolate (8a)



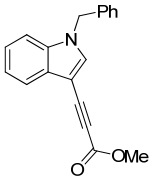
Following the general procedure, compound **8a** was isolated in 46 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35-7.27 (m, 3H), 7.20-7.18 (m, 2H), 6.82 (dd, *J* = 2.5, 1.6 Hz, 1H), 6.72 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.18 (dd, *J* = 3.9, 2.5 Hz, 1H), 5.19 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 137.6, 129.4, 128.6, 128.1, 127.5, 126.6, 121.2, 110.2, 87.7, 80.9, 53.1, 52.3. IR (film): $\tilde{\upsilon}$ = 2954, 2216, 2196, 1702, 1496, 1470, 1455, 1432, 1414, 1322, 1249, 1231, 1204, 1183, 1145, 1069, 1032, 725 cm^{-1}; GC-MS: *m/z* calcd for $C_{15}H_{13}NNaO_2$: 262.0838, found (M+Na): 262.0836.

Methyl 3-(1-benzyl-1H-pyrrol-3-yl)propiolate (8b)



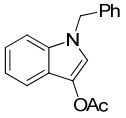
Following the general procedure, compound **8b** was isolated in 23 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35-7.30 (m, 3H), 7.11-7.08 (m, 3H), 6.59 (dd, J = 2.4, 0.3 Hz, 1H), 6.39 (dd, J = 2.4, 1.7 Hz, 1H), 5.03 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.7, 136.9, 129.6, 129.5, 128.8, 127.9, 122.6, 114.4, 101.5, 85.5, 81.2, 54.4, 53.0. IR (film): $\tilde{\upsilon}$ = 2954, 2361, 2335, 2209, 2193, 1698, 1433, 1372, 1249, 1227, 1199, 1149, 793, 744, 715 cm^{-1}.

Methyl-3-(1-benzyl-1*H*-indil-3yl)propiolate (10a)



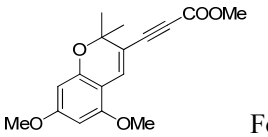
Following the general procedure, compound **10a** was isolated in 60 % yield ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82-7.80 (m, 1H), 7.55 (s, 1H), 7.35-7.23 (m, 6H), 7.16-7.14 (m, 2H), 5.32 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 135.8, 135.7, 135.6, 129.4, 129.0, 128.2, 127.1, 123.5, 121.6, 120.4, 110.5, 94.2, 84.1, 83.1, 52.5, 50.7. IR (film): $\tilde{\upsilon}$ = 2958, 2916, 2858, 2195, 1698, 1534, 1432, 1387, 1260, 1204, 739 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{19}H_{15}NO_2Na$: 312.0995, found: 312.0995.

1-Benzyl-1*H*-indol-3-yl-acetate (10b)[12]



Following the general procedure, compound **10b** was isolated in 12 % yield ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 7.9 Hz, 1H), 7. 34 (s, 1H), 7.32-7.25 (m, 4H), 7.21-7.17 (m, 4H), 5.37 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 137.2, 133.4, 129.8, 128.8, 127.7, 126.9, 122.6, 120.4, 119.6, 117.7, 117.3, 109.7, 50.1, 21.0.

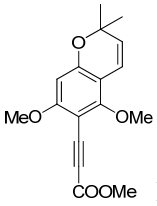
Methyl-3-(5,7-dimethoxy-2,2-dimethyl-2H-chromen-3-yl)propiolate (12a)



Following the general procedure, compound **12a** was isolated in 48% yield ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (s, 1H), 6.02 (d, J = 2.1 Hz, 1H), 6.00 (d, J = 2.1 Hz, 1H), 3.79 (s, 6H), 3.78 (s, 3H), 1.53 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 156.9, 155.2, 154.6, 130.7, 114.1, 104.5, 94.0, 91.9, 86.2, 82.8, 77.2, 55.6, 55.5, 52.6, 26.4. IR (film): $\tilde{\upsilon}$ = 2966, 2949, 2845, 2837, 2193, 1707, 1613, 1600, 1566, 1495, 1461, 1433, 1364,

1351, 1290, 1239, 1209, 1192, 1147, 870, 738 cm^{-1}; GC-MS (M+): *m/z*: calcd for $C_{17}H_{18}O_5$: 302.1, found: 302.4.

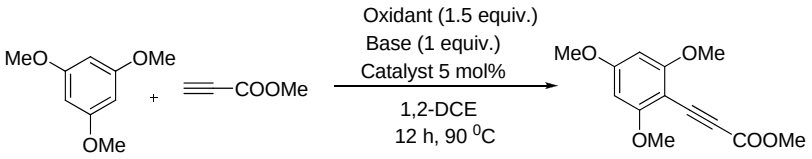
Methyl-3-(5,7-dimethoxy-2,2-dimethyl-2H-chromen-6-yl)propiolate (12b)



Following the general procedure, compound **12b** was isolated in 22% yield ^1H NMR (400 MHz, $CDCl_3$): δ = 6.52 (d, *J* = 9.9 Hz, 1H), 6.14 (s, 1H), 6.51 (d, *J* = 9.9 Hz, 1H), 3.98 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 1.43 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =164.0, 161.0, 158.1, 155.4, 128.1, 116.7, 108.4, 96.2, 95.4, 88.6, 81.9, 66.3, 62.7, 56.7, 53.0, 28.7. IR (film): $\tilde{\upsilon}$ = 2921, 2858, 2203, 1705, 1598, 1566, 1482, 1462, 1444, 1419, 1368, 1294, 1265, 1205, 1193, 1140, 1115, 1096, 870, 735, 704 cm^{-1}; GC-MS (M+): *m/z*: calcd for $C_{17}H_{18}O_5$: 302.1, found: 302.4.

2.5 Supplementary data

2.5.1 Further optimization reactions (cont. Table 1)[a]



1 **2a** **3a**

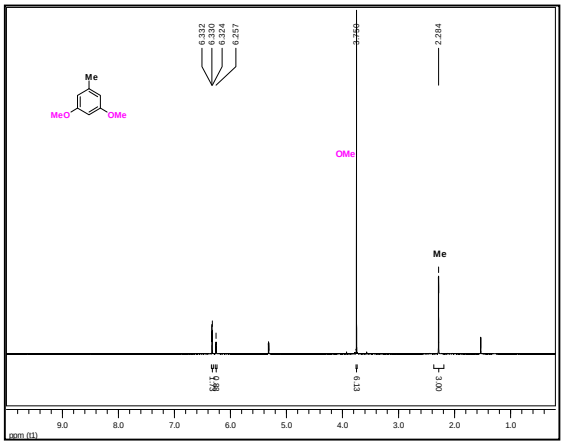
entry	catalyst	base	oxidant	Yield (%)[b]
1	$Ph_3PAuNTf_2$	K_3PO_4	$PhI(OAc)_2$	67
2	$Ph_3PAuNTf_2$	$CsCO_3$	$PhI(OAc)_2$	7
3	Ph_3PAuCl	Li_2CO_3	$PhI(OAc)_2$	55
4	Ph_3PAuCl	MgO	$PhI(OAc)_2$	64
5	$Ph_3PAuNTf_2$	K_2CO_3	PhIO	55
6	Ph_3PAuCl	K_2CO_3	PhIO	39
7	Ph_3PAuCl	K_2CO_3	$PhI(OCO(3,5\text{-dimethoxyphenyl}))_2$	45
8	Ph_3PAuCl	K_2CO_3	PIFA	0[c]
9	Ph_3PAuCl	K_2CO_3	$PhI(OAc)_2$	54[d]
10	Ph_3PAuCl	$NaHCO_3$	$PhI(OAc)_2$	75[d]

[a] Reactions carried out using **1** (2 equiv.), **2a** (1 equiv.), 1-1.5 equiv. of base, 1.5 equiv. of oxidant, 0.5 M at 90 °C in a sealed tube for 12 h. [b] Determined by GS-MS. [c] 2-Iodo-1,3,5-trimethoxybenzene is detected as major product. [d] The reaction was carried out in the microwave at 90 °C, 150 W for 40 min.

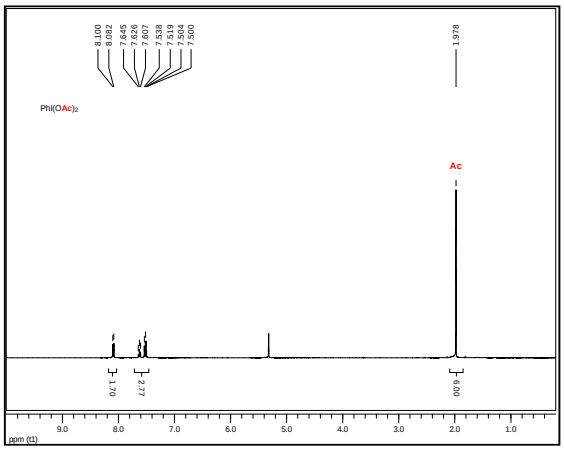
2.5.2 ^{1}H-NMR and ^{31}P-NMR mechanistic studies

2.5.2.1 Spectroscopic data of starting materials and other intermediates

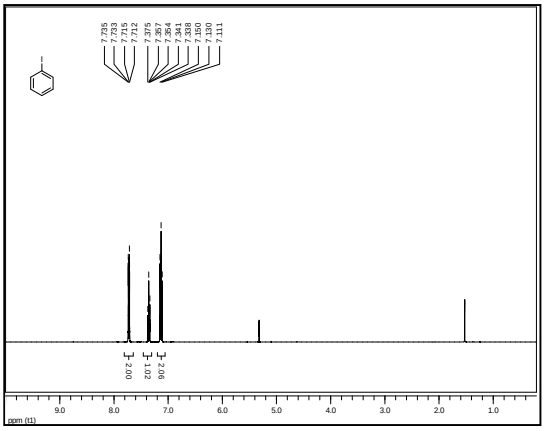
3,5-Dimethoxy-toluene (**5i**)



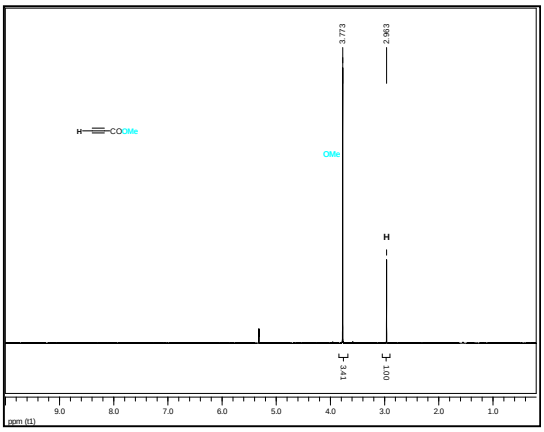
Iodobenzene diacetate PhI(OAc)$_2$



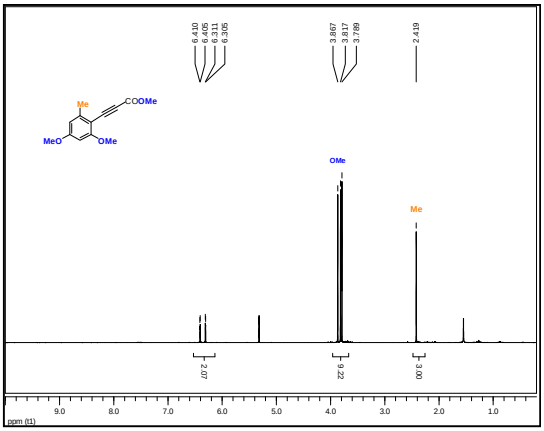
Iodobenzene



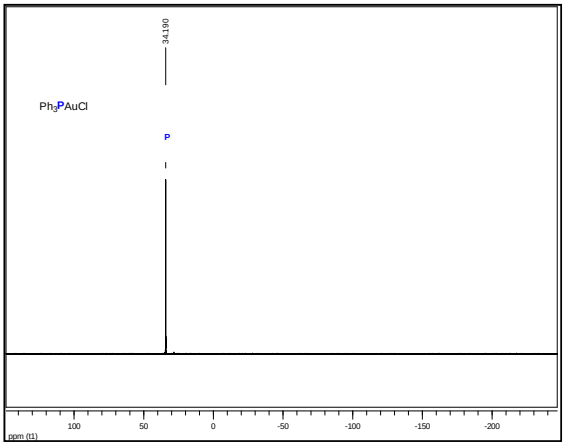
Methyl propiolate (**2a**)



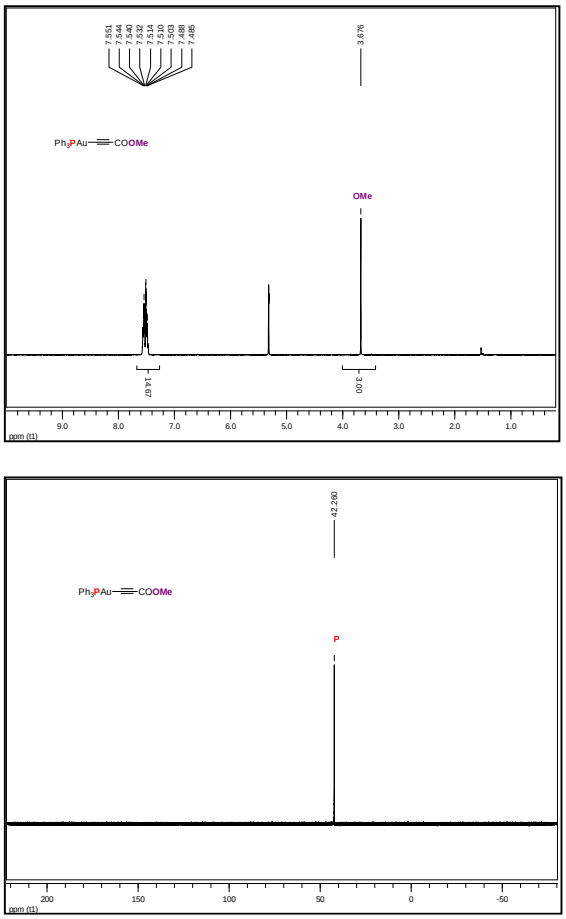
Methyl-3-(6-methyl-2,4-dimethoxyphenyl)-propiolate (**6i**)



Triphenylphosphine gold chloride (Ph_3PAuCl) (^{31}P NMR)



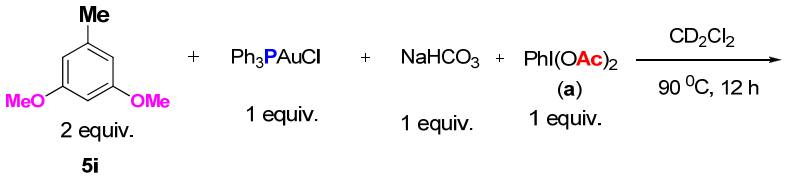
[(Methoxycarbonylethynyl)(triphenylphophine)gold] [(Ph_3P)Au(COOMe)] (I)[13]

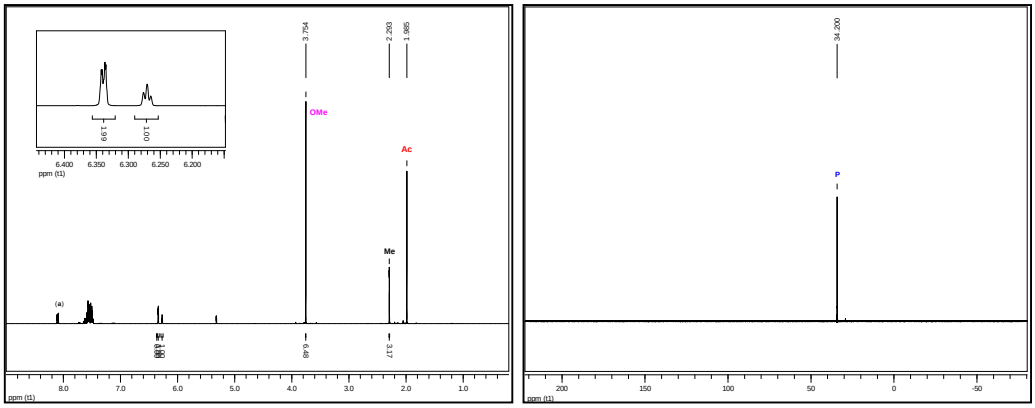


2.5.2.2 Detailed description of NMR experiments

Searching for aromatic auration

A reaction containing stoichiometric amounts of 1,3-dimethoxy-5-methyl benzene (**5i**), Ph_3PAuCl, $PhI(OAc)_2$ and $NaHCO_3$ in CD_2Cl_2 was performed in an NMR tube heating at 90 ºC. The reaction was controlled every 30 min for 12 h, showing no change in the aromatic signals of the starting materials by ^{1}H-NMR. The ^{31}P-NMR spectrum showed a single peak at 34.2 ppm, corresponding to the pure Ph_3PAuCl complex, thus ruling out the direct auration of the aromatic ring either by gold(I) or gold(III) species generated in situ from Ph_3PAuCl and $PhI(OAc)_2$.

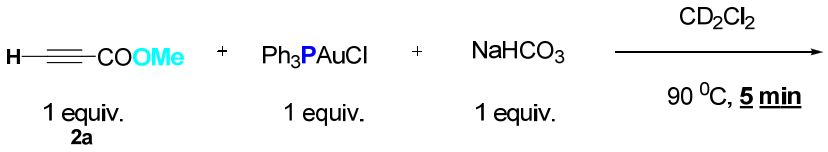


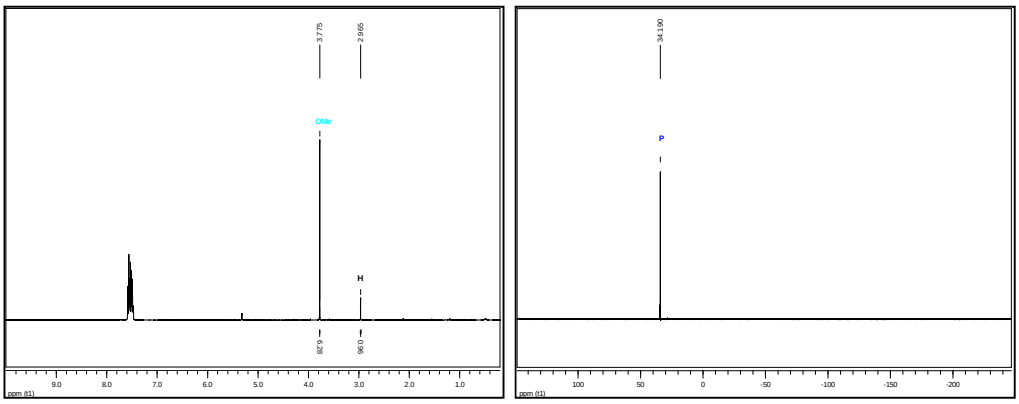


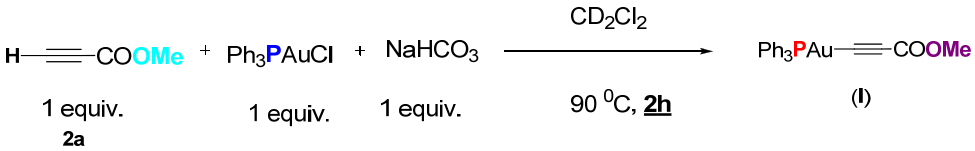
Searching for gold(I)-acetylide complexes

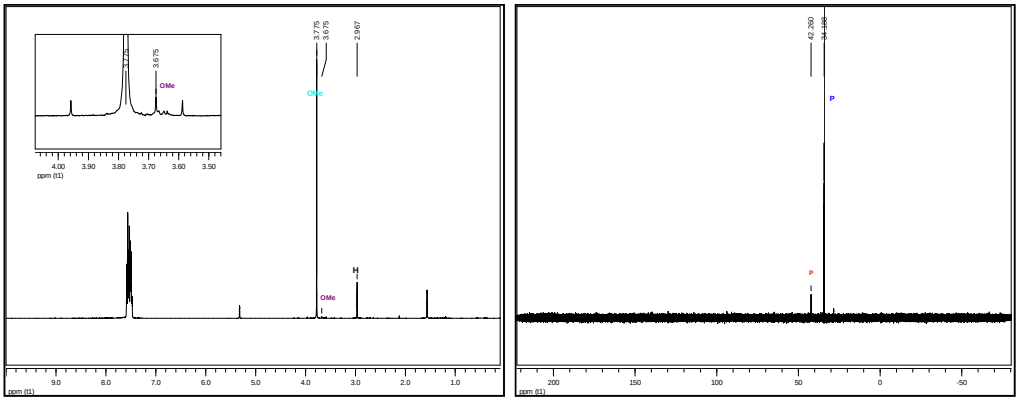
A reaction containing stoichiometric amounts of methyl propiolate (**2a**), Ph_3PAuCl and $NaHCO_3$ in CD_2Cl_2 was heated in an NMR tube to 90 ºC. After 5 min only starting materials were detected. After 2 hours, even if only in small amount, gold(I)-acetylide complex (**I**), prepared independently by other methods,[13] could be detected in both ^1H (**OMe**: 3.68 ppm) and ^{31}P-NMR (Ph_3**P**: 42.3 ppm) experiments. Formation of **I** requires the exchange of a chloride by an acetylide ligand which has to be formed in situ from **2a**, via π-activation of the alkyne with gold and proton abstraction with the weak base.[14]

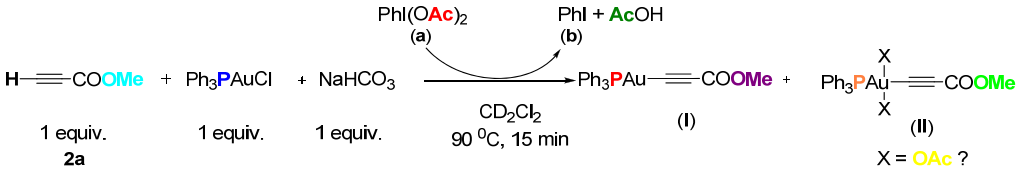
One equivalent of $PhI(OAc)_2$ was added to this mixture, and after only 15 minutes, a new peak at 31.6 ppm can be detected in the ^{31}P-NMR spectrum in addition to the ones of the pure complex and the gold acetylide (**I**) described above. Furthermore, the ^1H-NMR clearly shows a new methoxy peak (**OMe**) in addition to those of the free propiolate **2a** (**OMe**) and the gold(I)-acetylide (**I**) (**OMe**). A new signal at 2.2 ppm appears in the ^1H-NMR, which doesn't correspond neither to acetic acid nor to the pure $PhI(OAc)_2$. A tentative explanation involves the *in situ* formation of a gold(III)-acetylide complex (**II**) by oxidation of **I** with $PhI(OAc)_2$, which also would explain the appearance of iodobenzene in the ^1H-NMR of the reaction at this stage. It is not unreasonable to think that such gold(III) species, more electrophilic in nature, present signals for PPh_3 in a higher field of the ^{31}P-NMR spectrum than those of the analogous gold(I) complexes, as reported by Schmidbaur and co-workers.[15]

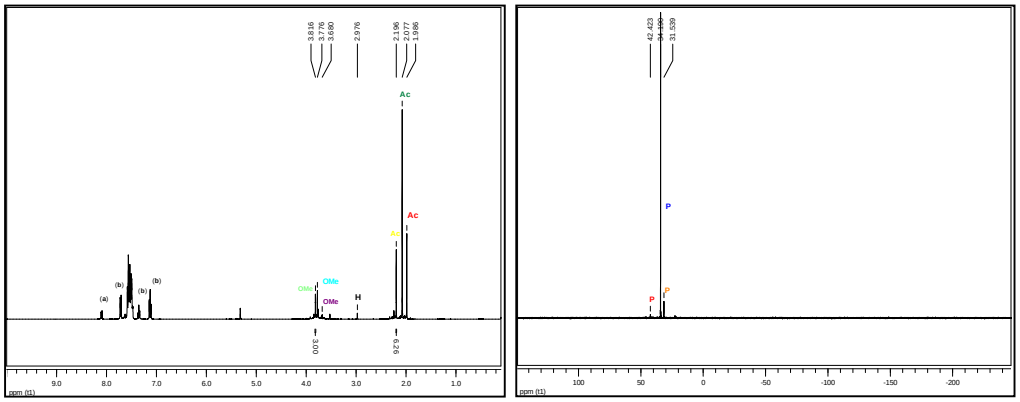

H—≡—COOMe + Ph3PAuCl + NaHCO3
CD2Cl2
90 0C, 5 min
1 equiv.
2a
1 equiv.
1 equiv.


3.775
2.965
OMe
H
34.190
P


H—≡—COOMe + Ph3PAuCl + NaHCO3
CD2Cl2
90 0C, 2h
Ph3PAu—≡—COOMe
1 equiv.
2a
1 equiv.
1 equiv.
(I)

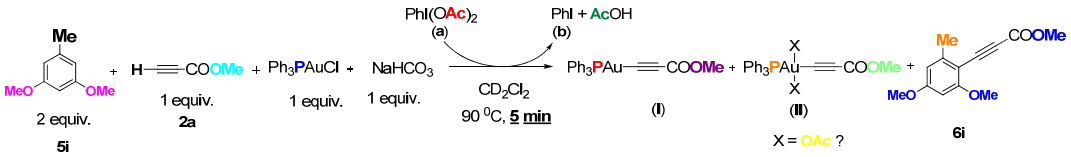

3.775
3.675
2.967
OMe
H
42.260
P

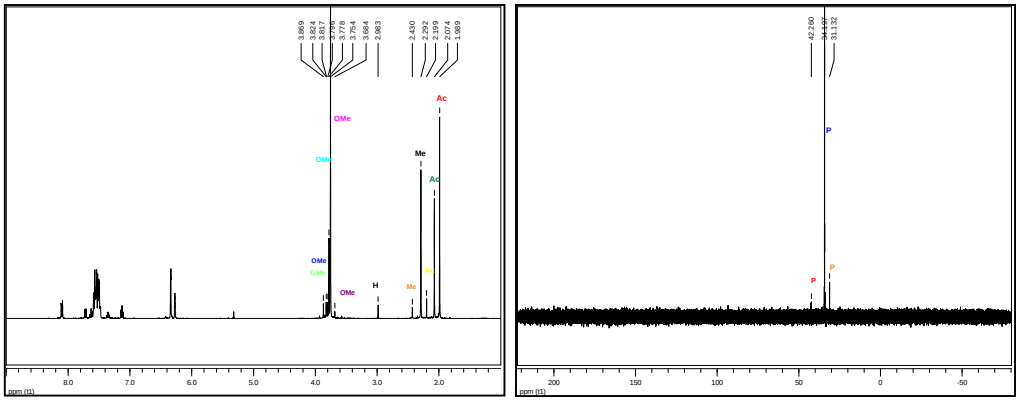




Searching for gold(I)-acetylide complexes in the presence of the aromatic counterpart

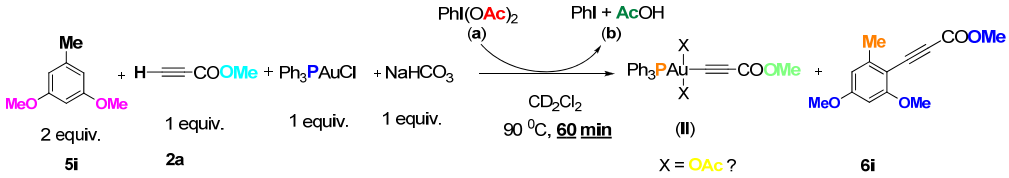
A reaction containing stoichiometric amounts of 1,3-dimethoxy-5-methyl benzene (**5i**), methyl propiolate (**2a**), Ph_3PAuCl, $PhI(OAc)_2$ and $NaHCO_3$ in CD_2Cl_2 was performed in an NMR tube heating at 90 ºC.

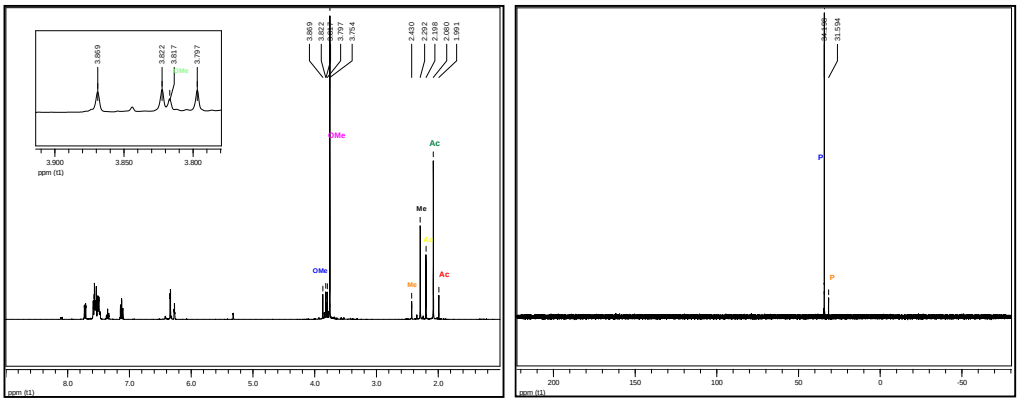




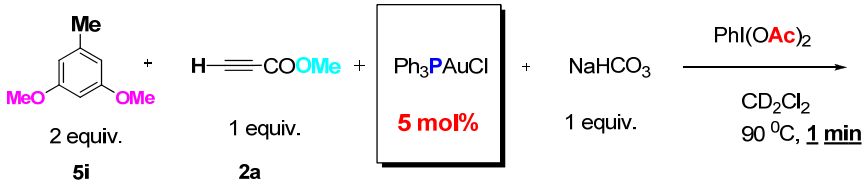
After only 5 minutes, the ^{1}H-NMR of the reaction already showed the formation of a small amount of (**I**) and the putative complex (**II**) in addition to the ethynylation product **6i**. Accordingly, the ^{31}P-NMR spectrum recorded at this stage contains the signals attributed to free complex Ph_3PAuCl (34.2 ppm), gold(I)-acetylide (**I**) (42.3 ppm) and gold(III)-acetylide (**II**) (31.5 ppm). Further progress of the reaction can be observed after 60 minutes, where

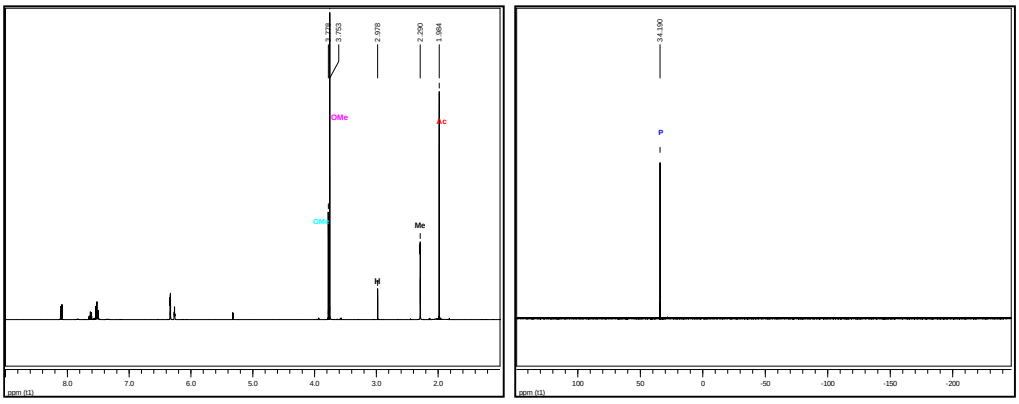
almost all the $PhI(OAc)_2$, propiolate **2a** and gold(I)-acetylide (**I**) have been consumed and only the signals of **5i**, iodobenzene, putative gold(III)-acetylide **II** and ethynylation product **6i** appear in both ^{1}H and ^{31}P-NMR spectra.



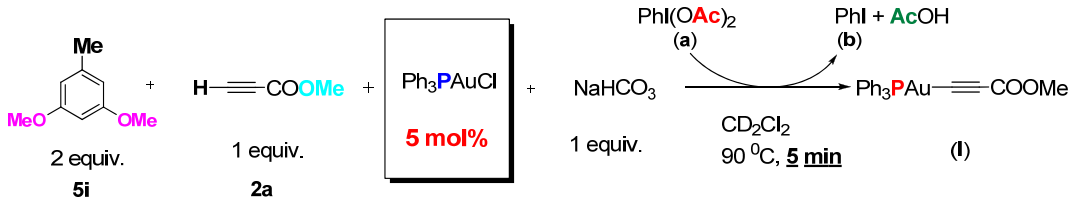


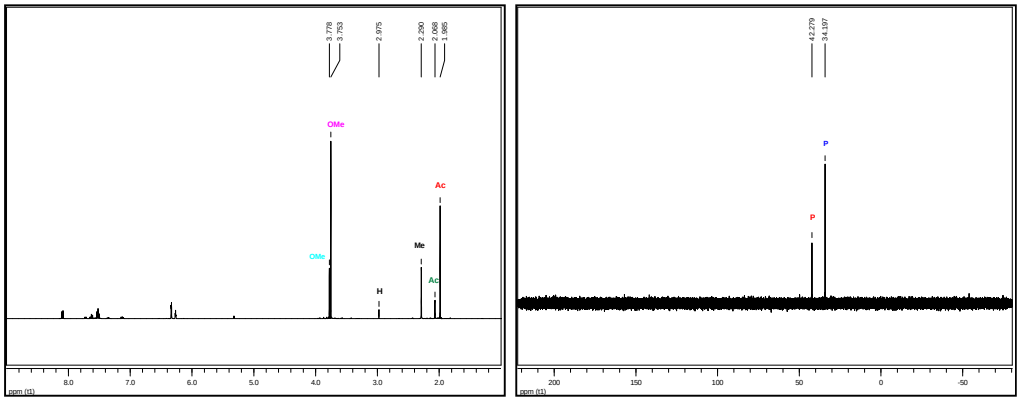
Finally, the same experiment was performed, now under the standard reaction conditions using **5i** (2 equiv.), **2a**, $PhI(OAc)_2$, $NaHCO_3$ (1 equiv.) and Ph_3PAuCl (5 mol%) in CD_2Cl_2 at 90 ºC.



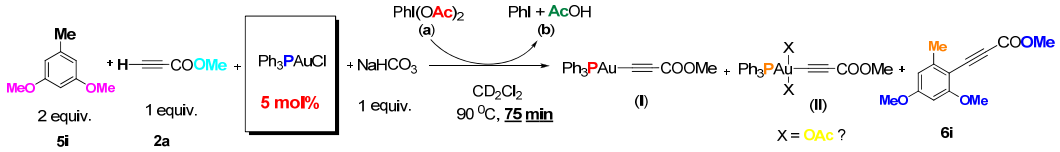


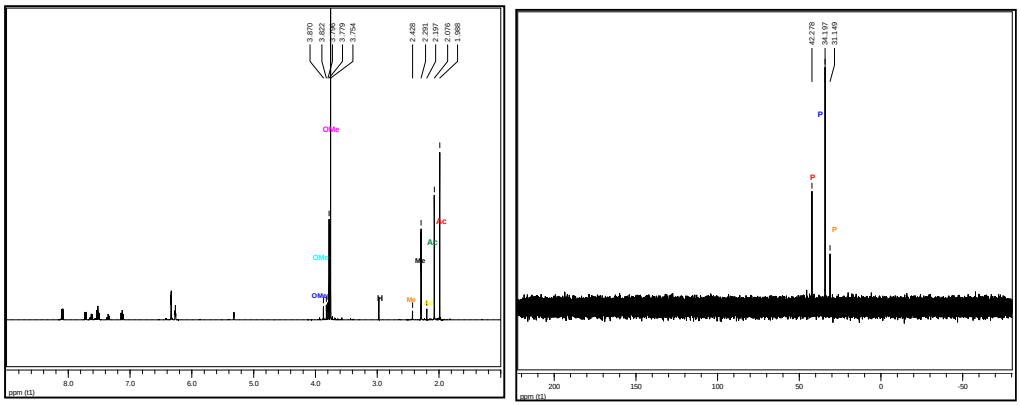
Initially, only the corresponding starting materials are observed. However, after only 5 min, gold(I)-acetylide (**I**) can be already detected in the reaction mixture (see ^{31}P-NMR).

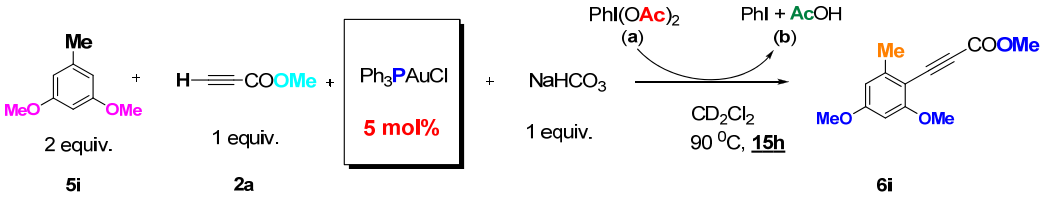


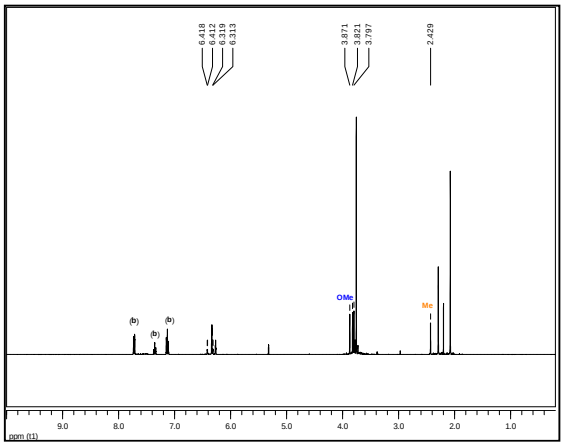


After 75 min, the three ^{31}P signals previously attributed to Ph_3PAuCl, (**I**) and (**II**) can be observed, and the ^{1}H-NMR already shows conversion of **5i** to ethynylated product **6i**, which is also observed in a larger extent in the ^{1}H-NMR recorded after 15 hours of reaction.









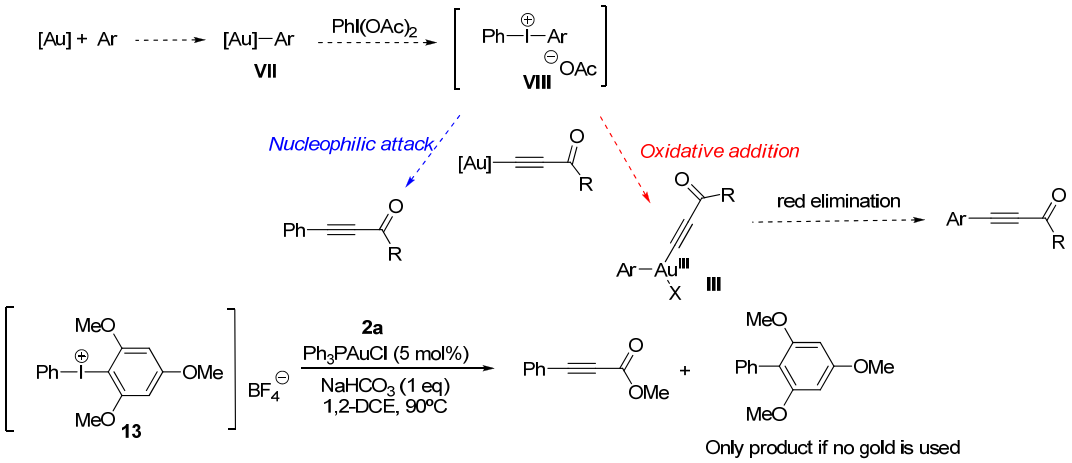
Our mechanistic proposal for the reaction tries to integrate the observations summarized above: we propose the formation of a gold(I)-acetylide complex (**I**) which undergoes oxidation in the presence of $PhI(OAc)_2$ to give complex (**II**). Stoichiometric auration of aromatic rings with gold(III) species has been previously reported,[16] although such complexes tend to aggregate in the absence of a suitable stabilizing ligand decomposing easily in solution. In our case, we assume that upon auration of the electron-rich aromatic ring, the reductive elimination step between the Csp^2 and Csp ligands on Au(III)-complex **III** occurs extremely fast, thus affording the observed ethynylation products and regenerating the Au(I) active catalytic species (Scheme 1, red path).

2.5.3 Additional mechanistic studies

2.5.3.1 Diaryl iodonium salts as intermediates

A different mechanism can be proposed, which involves the formation of diaryl iodonium salts (**VIII**) as potential reaction intermediates (Scheme 2).[17]

Scheme 2. Possible mechanism through diaryl-iodonium salts intermediate



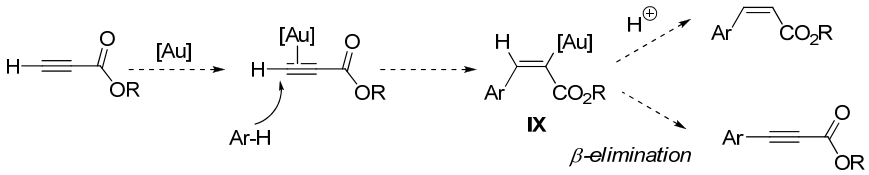
In such case, arene-gold species (**VII**) or the arene itself should react with $PhI(OAc)_2$ to form **VIII**. Then, if a simple nucleophilic attack from the gold(I)-acetylide (**I**) would occur, it should take place at the most electron-deficient site of the iodonium intermediate, forming phenyl propiolate, which was never detected in the reactions reported in the accompanying paper (Scheme 2, blue path). Furthermore, when compound **13**[17b] was treated with methyl propiolate (**2a**) in the presence of Ph_3PAuCl, and $NaHCO_3$, the only product detected was methyl 3-phenylpropiolate but only in trace amount. On the other hand, in analogy to previously described Sonogashira-type reactions with diaryl iodonium species,[18] a reaction mechanism could be envisioned where species such as **VIII** could undergo oxidative addition with gold(I) acetylide species to form intermediates **III** which might deliver the ethynylated products upon reductive elimination (Scheme 2, red path). A different sequence of steps such oxidative addition of Au(I) to **VIII** followed by transmetallation with Au(I)-acetylide would also be possible. In any case, the lack of reactivity of **13** makes these mechanistic hypotheses unlikely.

2.5.3.2 Elimination from vinyl-gold complexes

According to a previously reported gold(I)-hydroarylation reaction of electron-deficient alkynes by Reetz and co-workers,[19] coordination of a cationic gold complex to the alkyne and nucleophilic attack of the arene from the opposite side could lead to the formation of a putative vinyl-gold intermediate **IX** (not detected by ^{1}H-NMR), which would be

stereospecifically protonated to form the observed *Z*-olefins. Although not precedent for gold species, we envisaged that a *β*-elimination before the protonation event[20] could also produce the corresponding alkynes (Scheme 3).[21]

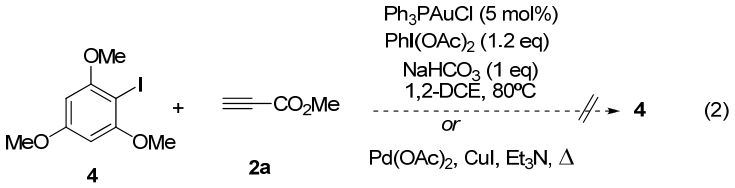
Scheme 3. Elimination from vinyl gold complexes



However, vinyl-gold **IX** have been recently reported and fully characterized as stable compounds.[22] The chemical shift of the vinylic protons is up to 8 ppm in the ^{1}H-NMR spectra and the ^{31}P shows a sharp signal at 44 ppm which is not in agreement with the NMR experiments described above.

2.5.3.3 Gold catalyzed Sonogashira reaction

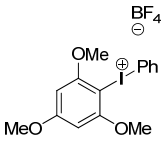
Since appreciable amounts of 2-iodo-1,3,5-trimethoxybenzene (**4**) were obtained in the reaction of **1** with **2a** (Table 1), we decided to test whether the formation of **3a** was just a combination of the iodination of the electron-rich arene with $PhI(OAc)_2$ followed by a gold-catalyzed "Sonogashira" reaction, analogous to the one recently reported by Corma and co-workers.[23] Under our standard reaction conditions (Table 1, entry 9), **4** could not be transformed into **3a**, ruling out this mechanistic hypothesis. Not surprisingly, even typical Pd-Cu catalyzed conditions delivered **4** unreacted, confirming the low reactivity of electron-rich aromatics towards oxidative addition (eq. 2).



(2)

2.5.4 Characterization of materials for the mechanistic studies

2,4,6-Trimethoxyphenyl(phenyl) iodonium tetrafluoroborate (11)



Compound **11** was prepared by addition of $BF_3{\cdot}Et_2O$ (0.33 mL, 2.64 mmol) to a solution of 2,4,6-trimethoxybenzenetributylstannane (1.0 g, 2.2 mmol)[24] in CH_2Cl_2 (20 mL) at 0 °C under N_2 atmosphere, and the mixture was stirred for 15 min. A solution of iodobenzene diacetate (0.850 g, 2.64 mmol) in CH_2Cl_2 (20 mL) was added at 0 °C and the mixture was stirred for 1 h. After the addition of a saturated aqueous solution of sodium tetrafluoroborate (10 mL) the mixture was stirred for 15 min. and then extracted with CH_2Cl_2, washed with water and dried over $MgSO_4$. Further purification by trituration using hexane-diethyl ether gave 2,4,6-trimethoxyphenyl(phenyl)iodonium tetrafluoroborate **10** (804 mg, 1.76 mmol) in 80% yield. ^{1}H NMR (400 MHz, DMSO): δ = 7.94 (dd, J = 8.3, 1.2 Hz, 2H), 7.63 (dt, J = 7.6, 1.2 Hz, 1H), 7.48 (t, J = 8.3 Hz, 2H), 6.48 (s, 2H), 3.96 (s, 6H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO): δ = 166.7, 159.8, 137.6, 134.8, 132.1, 116.5, 92.6, 87.4, 57.8, 56.6 HRMS (ESI): *m/z*: calcd for $C_{15}H_{16}IO_3$: 371.0138 found: 371.0140.

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Chapter 3

Mechanistic Insights on Gold-Catalyzed Alkynylation Processes

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Mechanistic Insights on Gold-Catalyzed Alkynylation Processes

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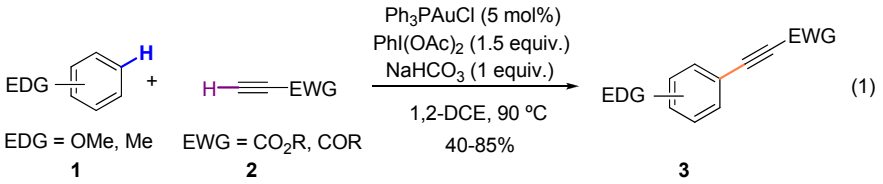
(*Manuscript for submission*)

3.1 Introduction

Aryl alkynes are a versatile intermediate in the synthesis of numerous natural products, bioactive molecules and organic materials.[1] Among the methods for the incorporation of acetylene groups into organic molecules, metal mediated cross-coupling reactions have a prominent role.[2] In particular, Sonogashira reaction, which involves terminal alkynes reacting with aryl or vinyl halides or triflates, has become the most important method for the synthesis of aryl alkynes and conjugated enynes.[3] While this transformation has found widespread applications, it suffers from several disadvantages. First, it requires the use of a prefunctionalized arene, which must be independently prepared adding one or more additional steps to a synthetic sequence. Second, if the aryl halide or triflate is electron rich, oxidative addition is more difficult making any cross coupling reaction extremely challenging.[4] Third, electron deficient alkynes poorly react with the aryl counterpart.[5]

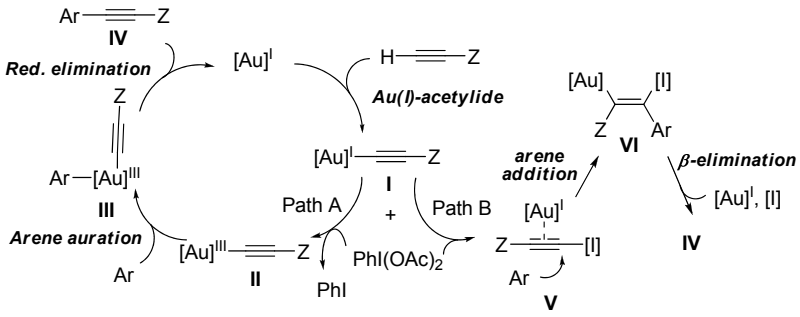
More recent efforts have begun to explore metal-catalyzed Csp^2-H bond activation as an alternative strategy for the construction of Csp-Csp^2 bond. This approach is attractive because it avoids the otherwise necessary prefunctionalization of the aromatic counterpart.[6] In contrast with the much more developed palladium catalyzed C-H arylation reactions,[7] direct C-H alkynylation of arenes has received much less attention. However, few examples have shown the viability of this approach. First, in 2010, Su and coworkers reported a Cu-catalyzed direct alkynylation of electron deficient polyfluoroarenes with terminal alkynes using O_2 as an oxidant.[8] Although this direct alkynylation of aromatic C-H bond with terminal alkynes appears quite attractive, the reaction is barely catalytic. A second example was reported by Waser and coworkers with a gold-catalyzed alkynylation of indoles, pyrroles and thiophenes where an alkynyliodine (III) reagent acts both as the alkyne source and external oxidant.[9] Finally, our group has reported a novel gold-catalyzed alkynylation of arenes via gold catalyzed C-H activation of both Csp and Csp^2-H bonds.[10] One of the most remarkable features of this protocol is the use of ‘‘deactivated’’ electron rich arenes (**1**) and electron

deficient alkynes (**2**) as coupling partners. In this work, Ph_3PAuCl in combination with the hypervalent iodine $PhI(OAc)_2$ as an external oxidant was found to be an effective catalytic system for the alkynylation reaction (eq. 1). Under the optimal reaction conditions, 1.5 equiv. of $PhI(OAc)_2$, 1 equiv. of $NaHCO_3$ and 5 mol% of Ph_3PAuCl at 90 °C in 1,2-dichloroethane, aromatic propiolates (**3**) were obtained in moderate to excellent yields. The reaction scope showed that arenes bearing electron-donating alkoxy groups or electron rich heteroaromatics such as indoles or pyrroles are well tolerated. On the other hand, various terminal alkynes with electron withdrawing groups such as esters or ketones afforded good reactivity. Notably, no biaryls resulting from oxidative homocoupling of the arene[11] or styrene products resulting from hydroarylation of the alkyne[12] were observed. In addition, these reactions proceeded efficiently in the presence of air and therefore the use of inert atmosphere was not required.



Based on NMR experiments where the formation of gold(I)-acetylide (**I**) was observed as a first intermediate in the reaction, two possible catalytic cycles were proposed as depicted in Scheme 1.

Scheme 1. Mechanistic proposal for the Au-catalyzed ethynylation of arenes



The first mechanistic proposal invokes a gold(I)/gold(III) catalytic cycle. After formation of the gold(I)-acetylide (**I**), oxidation with $PhI(OAc)_2$ could form the gold(III)-alkynyl complex **II**.[13] The reaction of the arene with complex **II** may occurs either by electrophilic aromatic substitution or by aromatic C-H activation[14] to give the arene aurate intermediate **III**. Finally, upon reductive elimination, the new Csp^2-Csp would be formed (Scheme 1, path A). Alternatively, in analogy to Waser's reports,[9] $PhI(OAc)_2$ could react with the gold(I)-acetylide (**I**) forming an alkynyl-iodonium intermediate (**V**). Activation of the alkyne by the gold complex would lead to arene addition forming a vinyl gold intermediate **VI**, which upon *β*-elimination would afford the aryl alkyne **IV** (Scheme 1, path B).

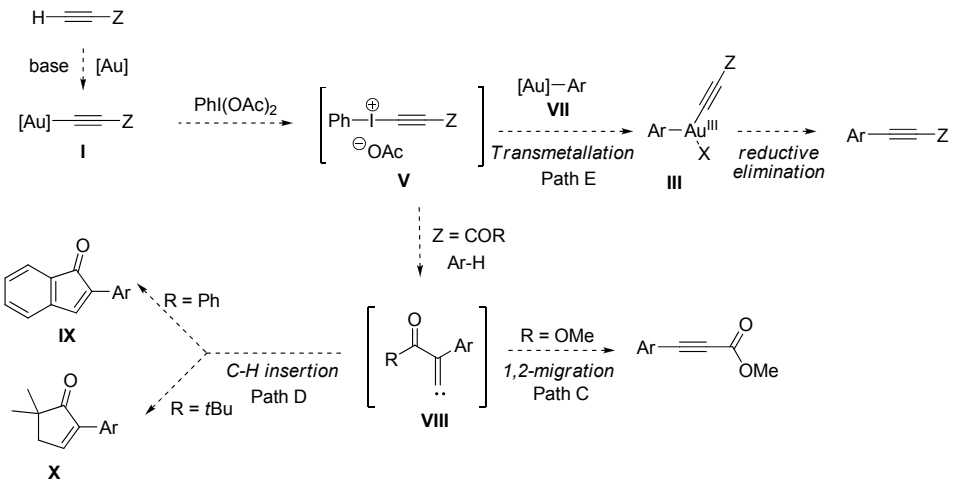
We present here a detailed mechanistic investigation on this transformation involving stoichiometric studies on potential reaction intermediates, rate order determination of each reaction component and kinetic both inter- and intramolecular isotopic effects. The results have enabled a better understanding of the reaction mechanism revealing the gold(I)/(III) redox process as the rate determining step in this transformation. This work, which represents the first detailed mechanistic investigation on gold-mediate oxidative cross coupling reactions so far, also provides interesting insights on the reactivity patterns governing gold-redox catalyzed processes.

3.2 Results and discussion

3.2.1. Mechanistic investigation towards alkynyl-iodonium salts as intermediate

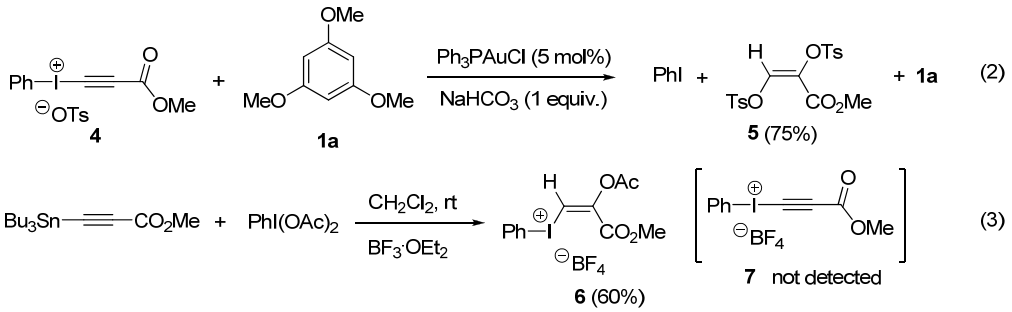
We decided to start our investigation with alkynyl-iodonium salts, which have been previously used as alkyne source in coupling reactions with organo-copper,[15] organoboronic acids and organostannanes.[16] In addition to the mechanism shown in Scheme 1, (path B), we also considered other possible reactivities upon formation of alkynyliodonium intermediate (**V**).[17,18] The regioisomeric nucleophilic attack of the arene onto the activated alkyne would produce an alkylidene intermediate (**VIII**) (Scheme 2). Upon 1,2-migration of the aromatic group, the observed ethynylated products could be obtained (path C, Scheme 2).[19] Alternatively, in the case of aromatic and alkylic ketones, insertion of the carbene into a proximal Csp^2 or Csp^3-H bond could also afford cyclopentenones **IX** and **X** respectively, as previously observed by Stang[20] and Taniguchi[21] (path D, Scheme 2). A third possibility would involve a transmetalation between iodonium salt **V** and gold-arylated species (**VII**) previously reported by Fuchita and co-workers[22,23], thus delivering intermediate **III**, which would yield the observed ethynylation products after reductive elimination (path E, Scheme 2).[24]

Scheme 2. Possible mechanism through alkynyl-iodonium salts intermediate



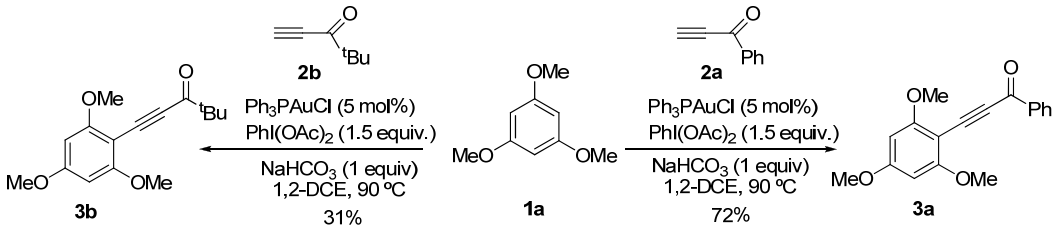
We tried to obtain experimental evidence for intermediates of type **V** without success. Precedents indicated that alkynyliodonium salts with electron-withdrawing groups (EWG) in the acetylenic moiety (**V**) are not stable and have to be handled at 0-20 ºC.[17] After extensive experimentation, iodonium salt **4** could be prepared according to previously reported procedures (Scheme 3).[17] Upon treatment with 1,3,5-trimethoxybenzene (**1a**), Ph_3PAuCl, and $NaHCO_3$, the only product isolated from the reaction mixture was (*E*)-methyl 2,3-bis(tosyloxy)acrylate **5** in 75% yield (eq. 2).[25] We decided to investigate the role of the counteranion, and attempted the synthesis of the tetrafluoroborate iodonium salt (**7**) from methyl-3-(tributylstannyl)propiolate and $PhI(OAc)_2$. However, **7** seemed to be too unstable to be isolated. Instead, nucleophilic attack of an acetoxy group onto the activated acetylenic moiety took place to give vinyliodonium salt **6** in 60% yield (eq. 3).

Scheme 3. Reaction experiments in presence of alkynyl iodonium salts.



Further evidence to rule out **V** as intermediate in these transformations was obtained from the reaction of phenyl- or *tert*-butyl alkynyl ketones **2a** and **2b** (Scheme 4). In contrast to previous reports,[22,23] no C-H insertion products were detected in these reactions (**X, XI** in Scheme 2, Path D).

Scheme 4. Ethynylation reaction of 1,3,5-trimetoxybenzene **1a** with alkynes **2a** and **2b**



In summary, the highly unstable nature of intermediates of type **V** and the lack of any C-H insertion products (**IX, X**) led us to rule out the participation of alkynyl iodonium species as intermediates in the alkynylation reaction reported in our previous work.

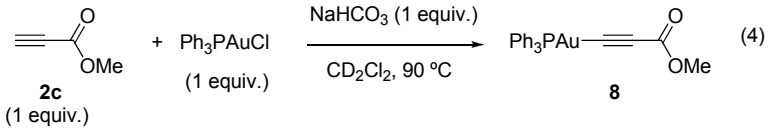
3.2.2. Gold(I)/gold(III) catalysis: Mechanistic investigation

We next sought to gain a detailed mechanistic understanding of this gold catalyzed oxidative cross-coupling reaction by means of stoichiometric studies as well as investigations of the reaction´s kinetics.

3.2.2.1 Stoichiometric Studies

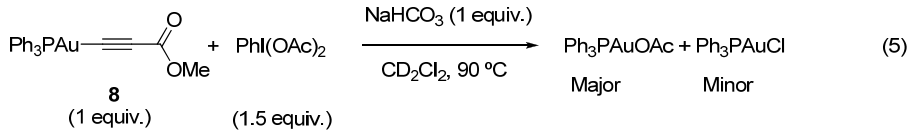
3.2.2.1.1 Formation of gold(I) acetylide (**I**): Confirmed

In our previous work, we showed the formation of gold(I)-acetylide (**I**) by ^{31}P NMR spectroscopy.[10] The reaction of methyl propiolate (**2c**) with stoichiometric amount of Ph_3PAuCl in CD_2Cl_2 at 90 °C afforded a new peak at 42.3 ppm in ^{31}P NMR and a new methoxy signal at 3.67 ppm in ^{1}H NMR, which was attributed to the gold(I)-acetylide **8** by comparison with a pure sample of this complex synthetized independently[26] (eq. 4). Interestingly, when the same reaction was carried out in the presence of $PhI(OAc)_2$ the formation of the gold complex **8** occurred faster than before, indicating that the oxidant activate the alkyne towards deprotonation. Furthermore, in the catalytic reaction of 3,5-dimethoxy toluene (**1b**) with methyl propiolate (**2c**) the formation of the corresponding gold(I)-acetylide (**8**) was confirmed by ^{31}P and ^{1}H NMR.



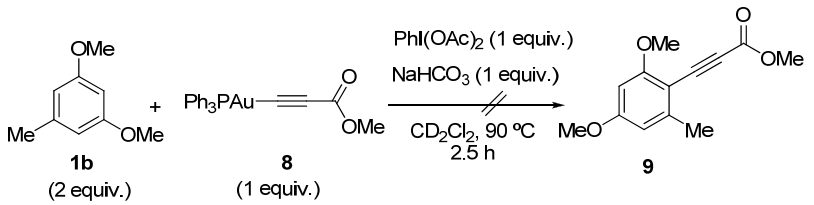
3.2.2.1.2 Formation of gold(III) acetylide (**II**):

According to the proposed catalytic cycle (path A in Scheme 1), gold(I)-acetylide (**I**) is oxidized by $PhI(OAc)_2$ to a gold(III) intermediate (**II**). In our previous report, the observation of a new signal at 31 ppm in the ^{31}P NMR upon heating a mixture containing $PhI(OAc)_2$, Ph_3PAuCl, methyl propiolate (**2c**) and sodium bicarbonate in CD_2Cl_2 at 90 ˚C, prompted us to propose that this new signal belonged to such gold(III) species, which would be indeed the productive intermediates in these transformations. To confirm this hypothesis, we treated gold(I)-acetylide (**8**) with $PhI(OAc)_2$ in CD_2Cl_2 and monitored the reaction by ^{1}H and ^{31}P NMR. However, the peak at 31 ppm was not observed. Indeed, low conversion of **8** was obtained and the new products detected in this transformation were $Ph_3PAuOAc$ and Ph_3PAuCl. The latest, which was formed as a minor product, indicates the activation of the solvent by the gold complex (eq. 5).[27]



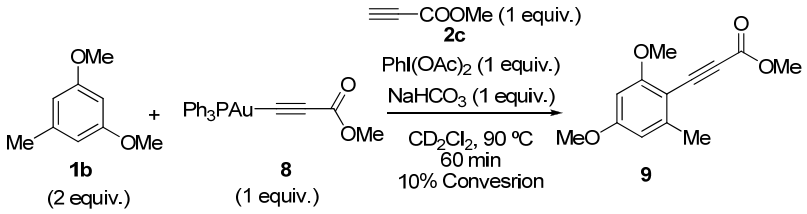
(5)

After this unexpected result, we decided to run the alkynylation reaction of 3,5-dimethoxy toluene (**1b**) using stoichiometric amount of gold (I)-acetylide (**8**) as alkynylating agent, in the presence of $PhI(OAc)_2$ and $NaHCO_3$ (eq. 6). Nevertheless, only traces of the aryl alkyne product **9** were detected in the reaction mixture after 2.5 h at 90 °C. Once again, **8** was transformed into $Ph_3PAuOAc$ and Ph_3PAuCl.[28]

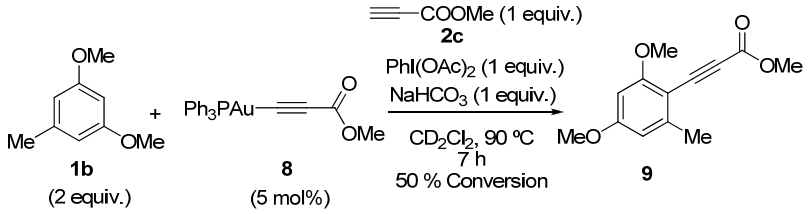


(6)

However, when free methyl propiolate was incorporated in the reaction, the formation of the product **9** was clearly observed after one hour[29] and the phosphorus signal at 31 ppm was detected after only 10 min (eq. 7). Furthermore, a catalytic version of this reaction using gold(I)-acetylide **8** as catalyst afforded 50% conversion to the product **9** after 7 hours (eq. 8).[27] These experiments suggest that free alkyne is required to obtain the intermediate species displaying a 31 ppm signal in the ^{31}P NMR.

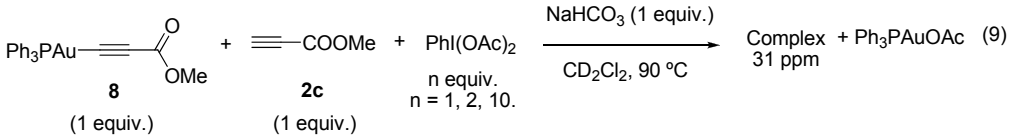


(7)



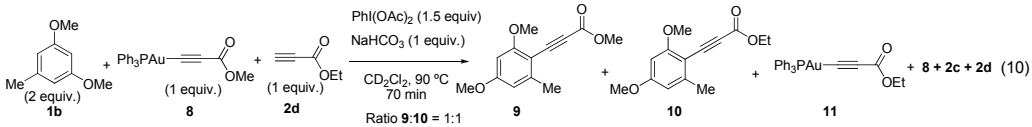
(8)

We then repeated the experiment showed in the eq. 5 but with 1 equiv. of free methyl propiolate (**2c**). In this case the formation of the complex at 31 ppm was also observed (eq. 9).[27] The addition of more equivalents of oxidant afforded an increasing conversion to $Ph_3PAuOAc$.



(9)

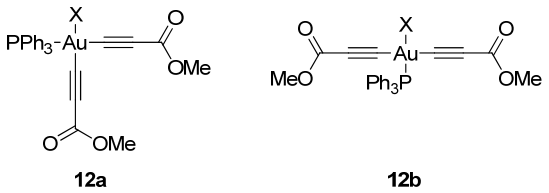
Further evidence for the need of free alkyne in these transformations was obtained when ethyl propiolate (**2d**) was added to a mixture of 3,5-dimethoxy toluene (**1b**), sodium bicarbonate, $PhI(OAc)_2$ and stoichiometric amount of gold(I)-acetylide **8** (eq. 10). Upon heating at 90 °C in CD_2Cl_2 for 70 min, a mixture of the ethynylated products **9** and **10** was detected in the reaction mixture. Moreover, only after 10 min a new gold(I)-acetylide **11** and free methyl propiolate were observed, which remarks the ability of gold(I)-acetylide to undergo ligand exchange.[27]



(10)

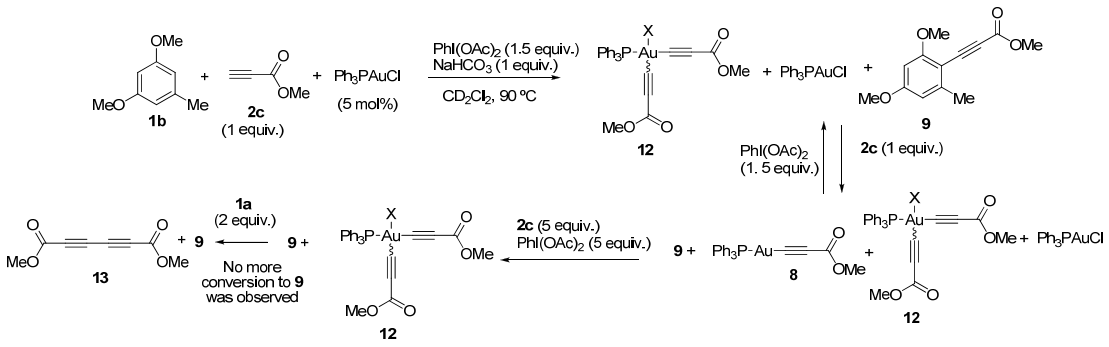
With this results in hand we sought to investigate whether the species detected in the ^{31}P NMR of our catalytic reaction were the productive intermediates along the catalytic cycle and whether or not these species, which seem to be produced only in the presence of free alkyne, could be due to the formation of gold(III)-bisacetylide complexes *cis*-**12a** or *trans*-**12b** (Figure 1).

Figure 1. Gold(III) bisacetylide *cis*-**12a** or *trans*-**12b** complexes



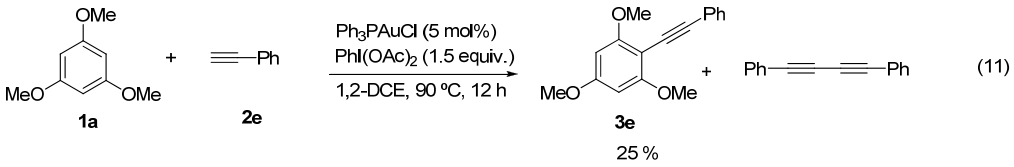
In a sealed NMR tube, the reaction of **1b** with methyl propiolate (**2c**), $PhI(OAc)_2$, $NaHCO_3$ in the presence of 5 mol% Ph_3PAuCl was heated at 90 °C. After 25 hours, alkynylation product **9** is observed and the oxidant was totally consumed. The gold(I)-acetylide **8** was not detected anymore by ^{31}P NMR and only Ph_3PAuCl and the complex with a ^{31}P signal at 31 ppm were observed (Scheme 5). Then, 1 equivalent of methyl propiolate (**2c**) was added to the reaction mixture. Interestingly, 40 min later, gold-acetylide **8** was the major gold complex in the reaction mixture. Then, 1.5 equiv. of oxidant was added affording the disappearance of the gold-acetylide **8** and only Ph_3PAuCl and the signal at 31 ppm in the ^{31}P NMR were detected. After continued addition of alkyne **2c** and oxidant, the specie with a ^{31}P signal at 31 ppm was obtained as single gold complex in the reaction.[30] However, the addition of 1,3,5-trimethoxybenzene (**1a**) to this reaction mixture did not afford any further conversion to the product. Interestingly, the homocoupling of the alkyne (**13**)[28] was observed, which could be explained by reductive elimination in **12** (Scheme 5).[27]

Scheme 5. Towards the activity of complex **12**



This experiment confirmed that the gold complex with a phosphorus signal at 31 ppm, is not the direct precursor of the product in the reaction, but rather a steady state of catalyst during the catalytic cycle. This would explain the low conversion to the ethynylated alkyne when the reaction is done with stoichiometric amount of gold as the alkyne is consumed in the synthesis of the gold(III) bis-acetylide. On the other hand, when less electron deficient alkynes such as phenyl acetylene are used, the alkyne homocoupling product is formed as a

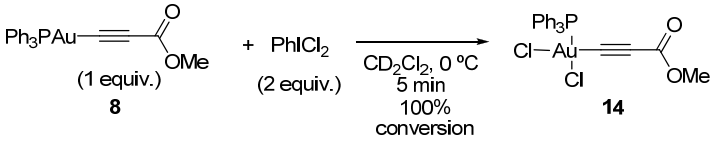
major product in the reaction (eq. 11). In this case, the formation of the gold(III)-bisacetylide must be favored as well as the reductive elimination to form the homocoupling product.[31]



However, these preliminary studies leave several key questions regarding the oxidation process. Although the reaction has been studied by NMR spectroscopic analysis, the active gold specie in this transformation is still unknown and could not be detected. Moreover, the oxidation of gold(I)-acetylide to a gold(III) intermediate could not been demonstrated due to the high reactivity of the productive gold species to undergo formation of the product.

To study the key oxidation step, we envisioned that the use of a different hypervalent iodine such as $PhICl_2$ could afford more stable gold(III)-acetylide complex. In fact, the formation of dichlorogold(III) complexes by oxidation reaction of gold(I) in presence of $PhICl_2$ has already been reported,[32] although it has never been applied to the oxidation of gold-acetylides. The reaction of **8** with 2 equiv. of $PhICl_2$ in CD_2Cl_2 at 0 °C gave almost total conversion to the dichloro-(triphenylphosphine)gold-acetylide **14** and traces of Ph_3PAuCl_3[32b,33] after only 5 min (Scheme 6).

Scheme 6. Oxidation of gold(I)-acetylide to dichlorogold(III)-acetylide (Scheme 6)

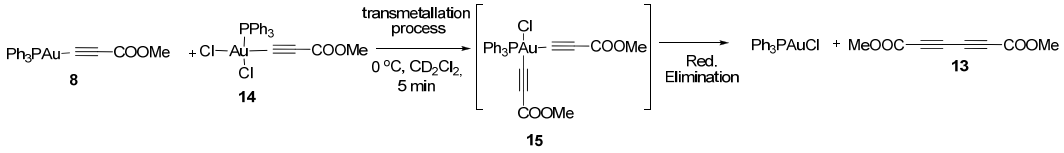


This complex was proved to be very unstable decomposing under common purification techniques such as column chromatography on silica gel, fluorosil or neutral alumina. Gratefully, when the reaction was carried out at low temperatures (< 0 °C) and cold pentane was added very slowly to the reaction mixture, yellow crystals of the complex were found in the solution after 24 hours and its structure, with the two chlorine ligands in *cis* disposition could be confirmed by X-Ray diffraction analysis.[34]

Interestingly, when the same reaction was carried out in the presence of only 1 equiv. of $PhICl_2$, a mixture of gold complex **14** and Ph_3PAuCl **(**detected by ^{31}P NMR) and the homocoupled alkyne **13** were observed by ^{1}H NMR. This experiment seems to indicate that if the oxidation of gold(I)-acetylide is not complete it will coexist in the reaction mixture with the gold(III)-acetylide species. Gold(I) and gold(III)-acetylide complexes can transmetalate to

form the gold intermediate **15**[35] which undergoes reductive elimination to lead homocoupling product **13** and Ph_3PAuCl (Scheme 7).

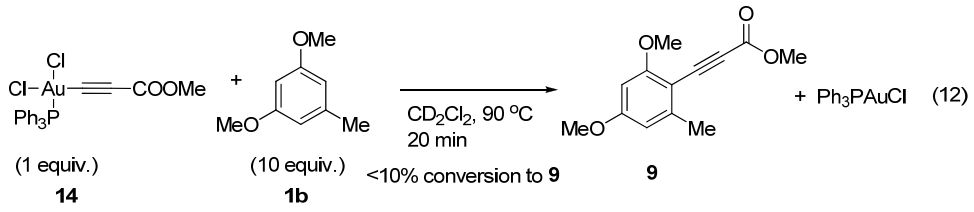
Scheme 7. Transmetalation process of gold(III)-acetylide with gold(I)-acetylide



The reaction of gold(I)-acetylide **8** with $PhICl_2$ led us to conclude that the oxidation of gold(I)-acetylide **I** to the gold intermediate **II** by an hypervalent iodine such as $PhICl_2$ or $PhI(OAc)_2$, is certainly possible although the new gold(III) complex **II** seems to be very reactive and could undergo decomposition extremely fast even at low temperatures and therefore it cannot be observed in the NMR spectroscopic analysis.

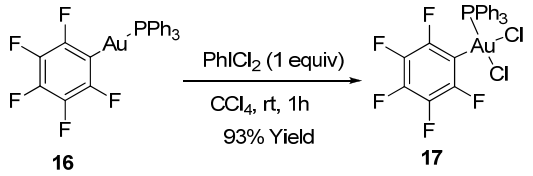
3.2.2.1.3 Synthesis of aryl alkynes from gold(III)-acetylide:

According to the mechanistic proposal outlined in the Scheme 1 (path A), the putative gold(III)-alkynyl complex should be the productive intermediate along the catalytic cycle. To test this hypothesis the dichlorogold(III)-acetylide **14** was treated with 3,5-dimethoxytoluene **1b** in CD_2Cl_2 at 90 °C. After 20 min only traces of ethynylated product and total conversion to Ph_3PAuCl were detected in the reaction mixture (eq. 12). The low conversion to the aryl alkyne can be explained by the instability of the gold complex **14** which, as it was mentioned before easily undergoes decomposition.

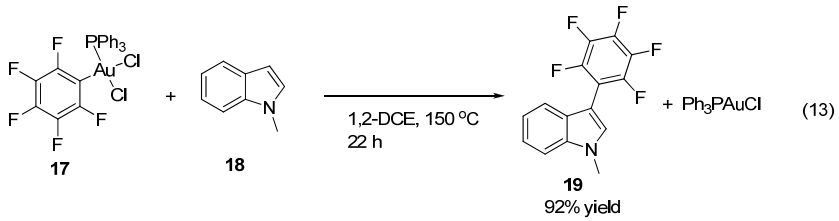


We then decide to study the arylation step in an analogous system. The propiolate ligand was substituted by electron deficient pentafluorobenzene ligand. Dichloro-(pentafluorophenyl)-(triphenylphosphine)-gold(III) **17** has already been reported starting from (pentafluorophenyl)-(triphenylphosphine)-gold(I) **16** in presence of $TlCl_3$ as oxidant.[36] Due to the toxicity of the thallium species we decided to oxidize complex **16** in the presence of $PhICl_2$ as we did previously. In this case, CCl_4 showed to be the solvent of choice and just one equivalent of oxidant was required (Scheme 8). The reaction afforded the *cis*-isomer exclusively as confirmed by X-ray diffraction[34] which could be isolated by direct filtration in 93% of yield.

Scheme 8. Oxidation of (pentafluorophenyl)-(triphenylphosphine)-gold(I) **16** in the presence of $PhICl_2$.



Gold complex **17** was treated with 1-methyl indole **18** in 1,2-dichloroethane at 150 °C for 22 hours affording the 1-methyl-3-(pentafluorophenyl)-indole **19** in 92% of yield as a single regioisomer. The detection of Ph_3PAuCl as a single gold complex in the reaction mixture confirmed that the cross coupling has occurred by reductive elimination in the gold(III) specie **17** (eq. 13).



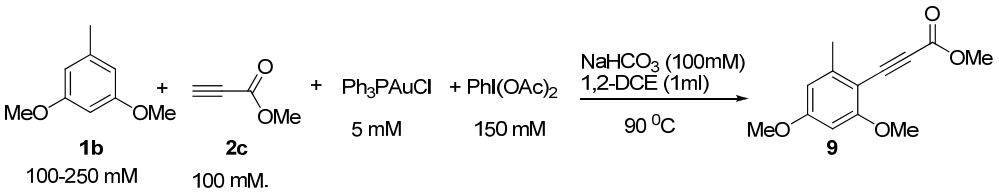
Although the reaction was studied by ^{31}P and ^{1}H NMR spectroscopy, the bisaryl-aurated species **III** could not be detected, which indicates that the formation of this gold(III) intermediate **III** and the reductive elimination must occurs extremely fast.

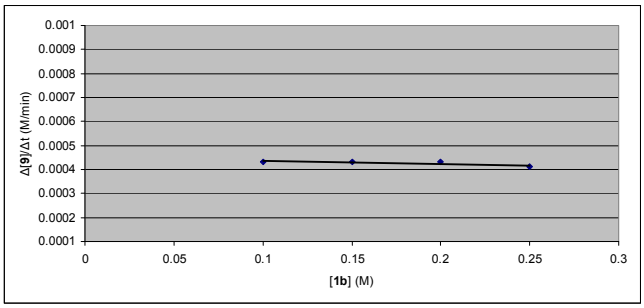
3.2.2.1 Kinetic Studies

3.2.2.1.1 Kinetic order of the reaction

We first sought to determinate the turnover-limiting step of this transformation by establishing the kinetic order in each reaction component. These studies focused on the Ph_3PAuCl catalyzed ethynylation of 3,5-dimethoxytoluene (**1b**) with methyl propiolate (**2c**) and $PhI(OAc)_2$. We first examined the order of this transformation in the arene by combining methyl propiolate (**2c**) (100 mM), $NaHCO_3$ (100 M), Ph_3PAuCl (5 mM) and varying concentration of **1b** (100-250 mM) in 1,2-dicloroethane (1 ml) at 90 °C. The reactions were monitored by gas chromatography and the initial rate method was used to determine the rate at each concentration of the substrate [**1b**].[27] As shown in Scheme 9, a plot of the initial reaction rate (Δ[**9**]/Δt) versus [**1b**] showed that the rate is independent of the concentration of the arene, indicating a zero-order dependence on the 3,5-dimethoxytoluene (**1b**).

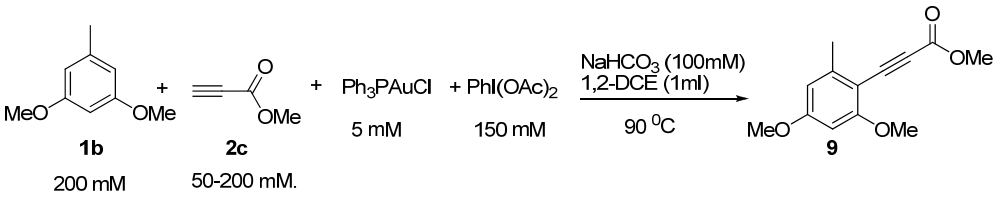
Scheme 9. Plot of initial rate (Δ[**9**]/Δt) versus [**1b**] showing a zero-order kinetics in [**1b**]

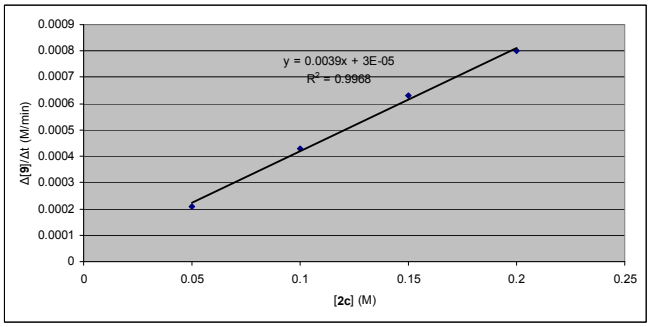




The order in the alkyne **2c** was next determined using an analogous procedure, with arene **1b** (200 mM), $PhI(OAc)_2$ (150 mM), $NaHCO_3$ (100 mM), Ph_3PAuCl (5 mM) and varying the concentration of **2c** (50-200 mM) in 1,2-DCE at 90 °C. As shown in Scheme 10, a plot of initial reaction rate Δ[**9**]/Δt versus [**2c**] was linear, indicating a first-order dependence on the alkyne.

Scheme 10. Plot of initial rate (Δ[**9**]/Δt) versus [**2c**] showing a first-order kinetics in [**2c**]

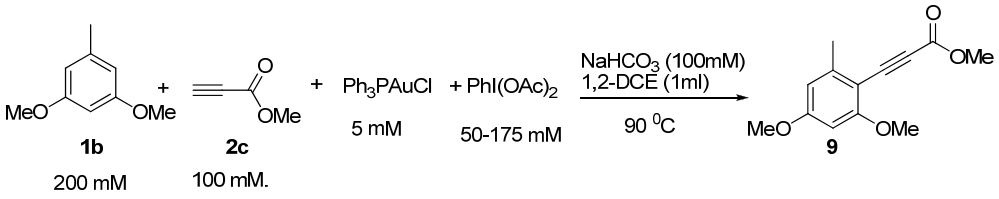


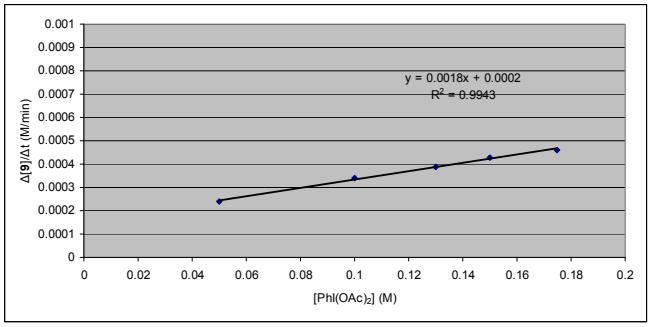


The order in the oxidant $PhI(OAc)_2$ was next examined using an analogous procedure, with arene **1b** (200 mM), **2c** (100 mM), $NaHCO_3$ (100 mM), Ph_3PAuCl (5 mM) and varying the concentration of $PhI(OAc)_2$ (50-175 mM), in 1,2-DCE at 90 °C. As shown in Scheme 11, a

plot of initial reaction rate Δ[**9**]/Δt versus [$PhI(OAc)_2$] was linear, indicating a first-order dependence on the oxidant.

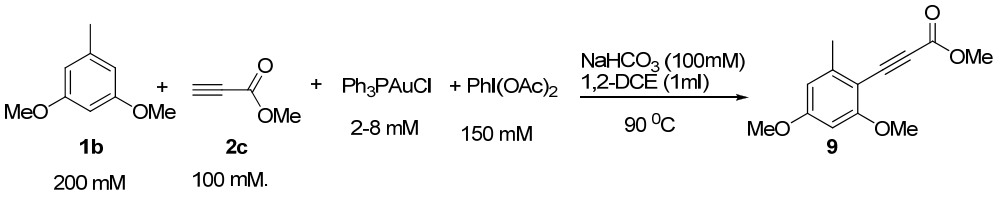
Scheme 11. Plot of initial rate (Δ[**9**]/Δt) versus [$PhI(OAc)_2$] showing a first-order kinetics in the oxidant.

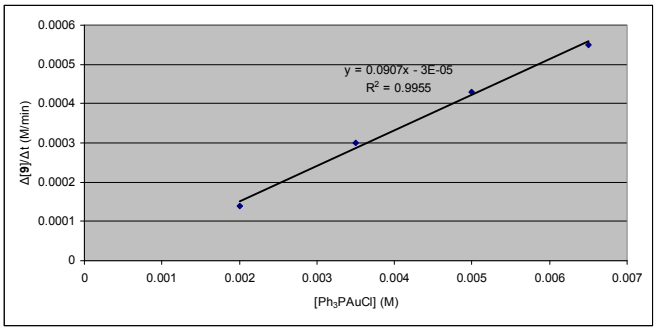




The reaction order in the catalyst, Ph_3PAuCl, was then determined, using 3,5-dimethoxytoluene (**1b**) (200 mM), methyl propiolate (**2b**) (100 mM), $NaHCO_3$ (100 mM), $PhI(OAc)_2$ (150 mM) along with [Ph_3PAuCl] ranging from 2 mM to 8 mM in 1,2-DCE at 90 °C. An excellent linear fit was observed for a plot of the initial reaction rate Δ[**9**]/Δt versus [Ph_3PAuCl] which indicate the first-order dependence in the catalyst (Scheme 12). This result is indicating that the active specie in the catalytic cycle is a monomeric catalytic complex.

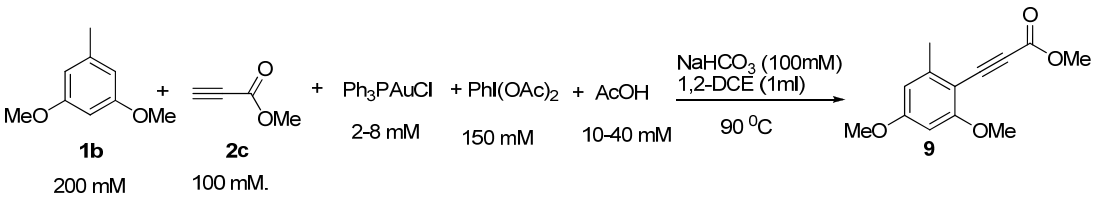
Scheme 12. Plot of initial rate (Δ[**9**]/Δt) versus [Ph_3PAuCl] showing a first-order kinetics in the catalyst.

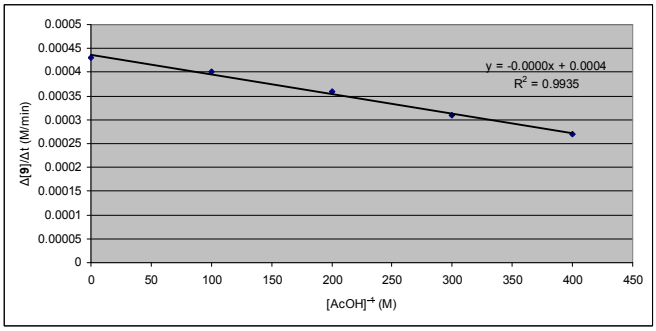




In order to understand the effect of the AcOH in the reaction, we measured the initial rates at different concentrations of acetic acid ranging from 10 to 40 mM. Arene **1b** (200 mM), **2c** (100 mM), $NaHCO_3$ (100 mM), Ph_3PAuCl (5 mM) and $PhI(OAc)_2$ (150 mM) and AcOH (10-40 mM) in 1,2-DCE at 90 °C were used. This transformation showed an inverse-first order dependence in AcOH, suggesting that AcOH is lost during the formation of a steady-state intermediate (Scheme 13).[37]

Scheme 13. Plot of initial rate (Δ[**9**]/Δt) versus [AcOH] showing an inverse first-order kinetics in [AcOH].



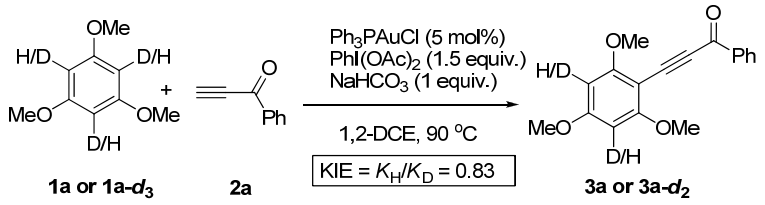


The fact that the reaction is first order on the catalyst, oxidant and alkyne indicates that the rate determining step of the ethynylation of arenes is the oxidation of gold(I)-acetylide (**I**) to gold(III) acetylide (**II**). This is in agreement with the detection by ^{31}P NMR of gold-acetylide **8** in the reaction mixture until the oxidant is consumed; thus complex **8** being the resting state of the catalyst throughout the reaction. Furthermore, in the oxidation step, $PhI(OAc)_2$ liberates AcOH which explains its inverse-first order dependence in the reaction. On the other hand, the order zero dependence observed in the arene is in agreement with the NMR spectroscopic analysis where aryl-aurate intermediate **III** could not be detected due to its high reactivity.

3.2.2.1.1 Kinetic isotope effect.

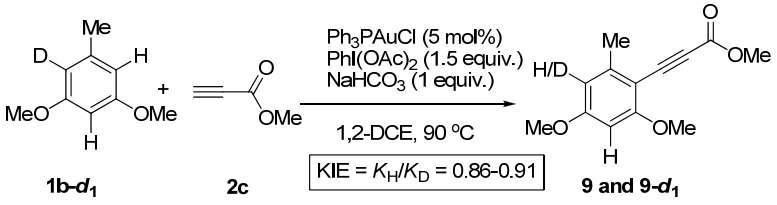
The primary intra- and intermolecular kinetic isotopic effects (K_H/K_D) for this C-H alkynylation reaction were determined. We first explored the intermolecular kinetic isotopic effect (KIE) for Ar-H activation by comparing the initial reaction rate for 1,3,5-trimethoxybenzene (**1a**) to that for **1a-*d*$_3$**[38] which was monitored by gas chromatography (Scheme 14).[39] The KIE was found to be 0.83, which indicates that the transition state does not involve Ar-H bond breaking.

Scheme 14. Intermolecular KIE for Ar-H activation.



We next determinate the primary intramolecular KIE for substrate **1b-*d*$_1$** based on ^{1}H NMR and MS spectroscopic analysis of the products formed in the reaction.[40] The intramolecular 1° K_H/K_D for **1b-*d*$_1$** was 0.91-0.86 (Scheme 15).[41]

Scheme 15. Intramolecular KIE for Ar-H activation.

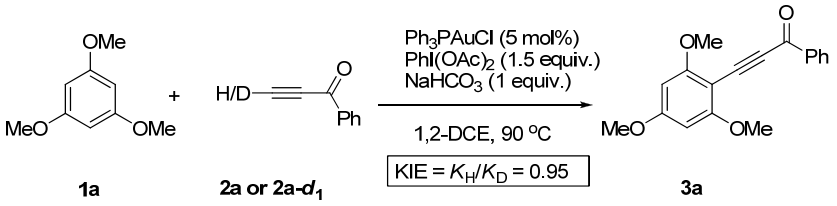


The subsequent reaction of the gold(III)-acetylide complex with the arene can be seen either as an electrophilic aromatic substitution or a C-H activation reaction. In the former case, the formation of a Wheland intermediate will exhibit, at most, a secondary isotope effect.[42] In contrast, if the C-H activation mechanism applies, one would expect a primary isotope effect

for breaking the C-X (X = H, D) bond.[43] In our case, an electrophilic aromatic substitution pathway seems to be involved in the reaction rather than a C-H activation process.

Finally we determined the 1° intermolecular kinetic isotopic effects for the C-H activation in the alkyne by comparing the initial reaction rate for phenyl acetylene (**2a**) to that for **2a-*d*$_1$**[44] which was monitored by gas chromatography (Scheme 16).[45] As shown in Scheme 15, the KIE was found to be 0.95.

Scheme 16. Intermolecular KIE for Csp-H activation.



1a **2a or 2a-*d*$_1$** **3a**

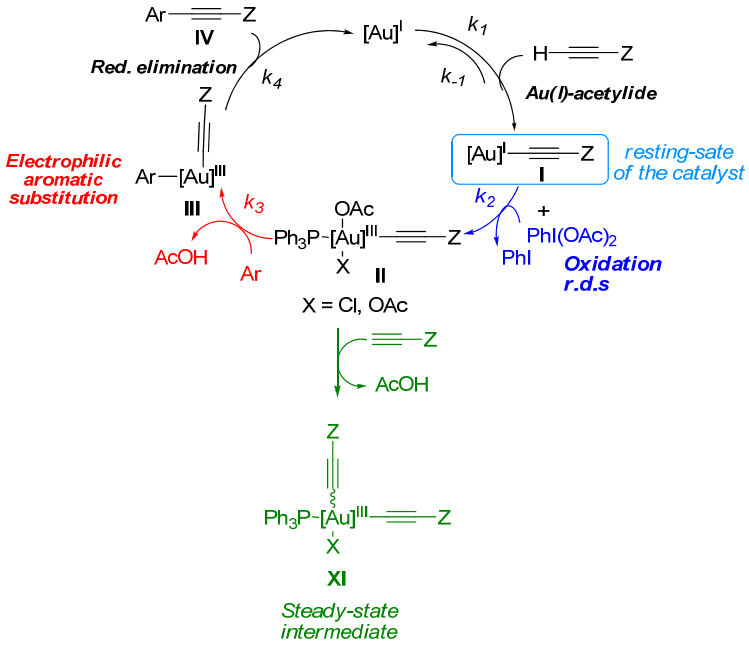
This result indicates that the step transforming the Csp-H into a Csp-Au(I) bond is not the rate limiting step of the reaction.

3.3 A new Mechanistic Proposal

The data collected above allow us to formulate a complete mechanistic picture of the catalytic alkynylation reaction. We propose that the gold(I)-acetylide (**I**) is the resting state of the catalyst. This proposal is consistent with the direct observation of gold complex **I** by ^{31}P NMR spectroscopy throughout the catalytic reaction until the oxidant is consumed. Interestingly, the reaction needs free alkyne to proceed, which is supported by all the stoichiometric experiments where gold(I)-acetylide were used as catalyst. To enter in the catalytic cycle, gold(I)-acetylide (**I**) is formed by the combination of free alkyne and Ph_3PAuCl. This transformation is favored in the presence of $PhI(OAc)_2$ which activates the alkyne towards deprotonation. The lack of the primary kinetic isotope effect on the alkyne (KIE = 0.95) indicates that the formation of the Au-Csp bond is not involved in the limiting turnover step. The reaction between gold(I)-acetylide (**I**) and $PhI(OAc)_2$ to afford a high oxidation state monomeric gold(III) intermediate **II** is proposed to be the rate determining step of the catalytic cycle according to the reaction kinetics, which is then followed by the aromatic auration to lead intermediate **III**. The observations of a secondary inter- and intramolecular kinetic isotopic effect in the arene is consistent with an electrophilic aromatic substitution rather than a C-H activation process. Finally, upon reductive elimination the ethynylated product is formed and the gold(I) specie is returned to the catalytic cycle. On the other hand, the putative intermediate **II** in the presence of free alkyne can undergo formation of gold complex **XI** with a signal at 31 ppm in the ^{31}P NMR, which seems to be the steady-

state of the catalyst as shown in the stoichiometric experiment depicted in Scheme 5, which is also supported by the observation of inverse first order in the AcOH.

Scheme 16. Mechanism proposal for the ethynylation of arenes



Based on the observations discussed above, a rate equation shown in eq. 14 can be proposed. Since the oxidation from gold(I) to gold(III) is the rate determining step, it determines the rate of the overall reaction. Application of the pre-equilibrium approximation for [gold(I)-acetylide] (eq. 15) affords the rate expression depicted in eq. 16.

$$rate = k_2[gold(I)-acetylide][PhI(OAc)_2] \qquad (14)$$

$$[gold(I)-acetylide] = \frac{k_1}{k_{-1}}[Ph_3PAuCl][Alkyne] \qquad (15)$$

$$rate = \frac{k_2 k_1}{k_{-1}}[Alkyne][Ph_3PAuCl][PhIOAc] \qquad (16)$$

The proposed rate equation of the reaction shown in eq. 16 with a first order in the oxidant, catalyst and alkyne is consistent with the experimental observations.

3.4 Conclusions

In summary, this work describes detailed mechanistic investigation of gold catalyzed cross coupling reactions between non-functionalized arenes and alkynes. A plausible reaction mechanism where alkynyl-iodonium intermediates are involved (Scheme 1, path B) could be ruled out based on experimental evidences.

Indeed, a mechanism involving the participation of gold(I)/gold(III) redox catalytic cycle was supported by stoichiometric and kinetic studies. The resting state of the catalyst was found to be gold(I)-acetylide (**I**) indicating that the oxidation process was the turnover limiting step of the catalytic cycle.

All the individual reaction steps for the proposed mechanism were investigated. The oxidation of gold(I)-acetylide by an hypervalent iodine could be demonstrated by the reaction of gold acetylide **8** with $PhICl_2$ which afforded the unstable *cis*-dichlorogold(III)-acetylide (**15**). On the other hand, the cross coupling reaction between stoichiometric pentafluorobenzenegold(III) specie **17** and 1-methyl indole afforded the hetero-diaryl product in 92% yield confirming the last steps of the catalytic cycle. This last study highlights the possible potential of other coupling partners as polyfluoroarenes in gold catalyzed cross coupling reactions. Finally, these investigations raise the larger question of what is the active specie in the ethynylation reaction which cannot be detected by NMR spectroscopy. In order to solve this question, MS spectroscopy analyses are in process and the results will be present in the due course.

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[30] The peak at 31 ppm in ^{31}P NMR was shifted to 32 ppm due to the increase concentration of AcOH in the solution.

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[35] Traces of the possible gold complex **15** were isolated after a column chromatography on silica gel together with Ph_3PAuCl. Different attempts to synthesize this complex by ligand exchange in the dichlorogold(III)acetylide **14** have not been successful.

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[39] Studies were performed mixing alkyne **2a** (1 equiv.), with deuterated arene **1a** or alternatively **1a-d_3** (2 equiv.), $PhI(OAc)_2$ (1.5 equiv.), Ph_3PAuCl (5 mol%) and $NaHCO_3$ (1equiv.) in 1,2-DCE heating at 90 ºC. See supplementary data.

[40] Studies were performed mixing alkyne **2c** (1 equiv.), with deuterated arene **1b-d_1** (2 equiv.), $PhI(OAc)_2$ (1.5 equiv.), Ph_3PAuCl (5 mol%) and $NaHCO_3$ (1equiv.) in CD_2Cl_2 heating at 90 ºC in a sealed NMR tube. See supplementary data.

[41] ^1H NMR spectroscopy of the purified mixture **9** and **9-d_1** shown a KIE = 0.86. MS spectroscopic analysis of the reaction mixture shown KIE = 0.91.

[42] Electrophilic aromatic substitution by carbon electrophiles shows no primary isotopic effect since proton transfer from Wheland intermediate is assumed to be fast (Taylor, R. Electrophilic Aromatic Substitution; John Wiley&Sons: New York, 1990). It was suggested that, in electrophilic aromatic substitutions involving strong electrophiles, small secondary isotope effects are to be expected, both directions and size being difficult to predict: Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1962**, *84*, 1688.

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[45] Studies were performed mixing arene **1a** (2 equiv.), with alkyne **2a** or alternatively **2a-d_1** (1 equiv.), $PhI(OAc)_2$ (1.5 equiv.), Ph_3PAuCl (5 mol%) and $NaHCO_3$ (1equiv.) in 1,2-DCE heating to 90 ºC. See supplementary data.

Chapter 3

Experimental Section

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3.5 General information

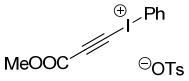
NMR spectra were recorded on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual ^{1}H and ^{13}C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution electrospray ionization mass spectrometry was performed on a Finnigan MAT 900 (Thermo Finnigan, San Jose, CA; USA) doublefocusing magnetic sector mass spectrometer. Ten spectra were acquired. A mass accuracy ≤ 2 ppm was obtained in the peak matching acquisition mode by using a solution containing 2 µl PEG200, 2 µl PPG450, and 1.5 mg NaOAc (all obtained from Sigma-Aldrich, CH-Buchs) dissolved in 100ml MeOH (HPLC Supra grade, Scharlau, E-Barcelona) as internal standard. GC-MS analysis was done on a Finnigan Voyager GC8000 Top.

GS analyses to measure the Kinetic of the reaction were done on a Trace GS 2000 series. The Column employed is a Zebron Phase: ZB-5, 30m x 0.25mm x df = 0.25µl. The Method employed to calculate the order of the reagents was 5 minutes at 40 ºC then 10 minutes at 250 ºC with an over-run time of 29 minutes. (rate (°C/min) = 15); The method employed to determinate the intermolecular kinetic isotopic effects in the arene **1a**/**1a**-d_3 and in the alkyne **2a**/**2a**-d_1 was 5 minutes at 60 ºC then 15 minutes at 300 ºC with an over-run time of 29 minutes. (rate (°C/min) = 15). Dodecane was used as an internal standard.

Materials and Methods: Unless otherwise stated, starting materials were purchased from Aldrich and/or Fluka. All reagents were used as received except for iodobenzene diacetate, which was recrystallized from an aqueous solution of acetic acid (5 M) and dried overnight under high vacuum.[1] Potassium carbonate and sodium bicarbonate was dried overnight at 80 ^{0}C. PPh_3AuCl was prepared according to previously reported procedures.[2] Solvents were purchased in HPLC quality, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Unless otherwise stated, reactions WERE NOT run under inert atmosphere. Conversion was monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. Flash column chromatography was performed over silica gel (230-400 mesh).

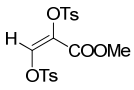
3.6 Characterization of products

Alkynyl(phenyl)iodonium tosylate (4)[3]



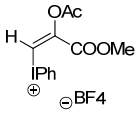
Under N_2 atmosphere, a solution of [(carbomethoxy)ethynyl]tributylstannane (322 mg, 1.03 mmol)[4] in dichloromethane (10 mL), was added dropwise to a stirred suspension of hydroxy(tosyloxy)iodobenzene in dichloromethane (392 mg, 1.0 mmol, 0.1 M) at – 42 °C. Stirring was maintained at – 42 ºC for 45 min followed by addition of an equal volume of diethyl ether (3 x 30 mL). The cruce solid was filtered and recrystallized immediately from dichloromethane/pentane and dried in under vaccum to get compound **7** (137 mg, 0.3 mmol) in 30 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 7.8 Hz, 2H), 7.59-7.43 (m, 5H), 7.09 (d, J = 7.8 Hz, 2H), 3.77 (s, 3H), 2.33 (s, 3H).

Methyl-1,3-ditosyl-2-propenoate (5)



Compound **8** was obtained by addition of PPh_3AuCl (3.0 mg, 0.006 mmol) to a solution of alkynyl(phenyl)iodonium tosylate (**7**) (57.0 mg, 0.125 mmol,), $NaHCO_3$ (11.0 mg, 0.13 mmol) and 1,3,5-trimethoxybenzene **1** (42.0 mg, 0.25 mmol) in 1,2-dichloroethane (0.9 mL). The mixture was stirred at 90 ºC for 12 h. Then, the reaction mixture was filtered under a pad of celite and purified by flash column chromatography in silica gel with Hexane: AcOEt (5:1) to give **8** (40 mg, 0.093 mmol) in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 1H), 7.69 (s, 1H), 3.73 (s, 3H), 2.47 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.2, 147.2, 146.2, 139.9, 133.7, 132.1, 130.8, 130.3, 129.0, 128.8, 127.0, 53.3, 22.4, 22.3.

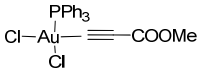
Alkenyl(phenyl)iodonium tetrafluoroborate (6)



Compound **10** was prepared by addition of $BF_3{\cdot}Et_2O$ (0.39 mL, 3.12 mmol) to a solution of [(carbomethoxy)ethynyl]tributylstannane (1.0 g, 2.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C under N_2 atmosphere and the mixture was stirred for 15 min. A solution of iodobenzene diacetate (1.0 g, 3.2 mmol) in CH_2Cl_2 (20 mL) was added at 0 °C and the mixture was stirred for an additional 1 h. After the addition of a saturated aqueous solution of sodium tetrafluoroborate (10 mL), the mixture was stirred for 15 min. and then extracted with CH_2Cl_2, washed with water and dried over $MgSO_4$. Further purification by trituration using hexane-diethyl ether gave alkenyl(phenyl)iodonium tetrafluoroborate **10** (675 mg, 1.5 mmol)

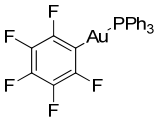
in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 7.5 Hz, 2H), 7.76 (s, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 3.83 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 157.9, 149.5, 136.1, 133.2, 132.6, 110.5, 99.2, 53.9, 19.9. HRMS (ESI): *m/z*: calcd for $C_{12}H_{12}IO_4$: 346.9774 found: 346.9773.

***cis*-Dichloro(triphenylphosphine)gold(III)acetylide (14)**



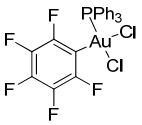
To a solution of gold(I)acetylide (1.0 equiv.) in CD_2Cl_2 at 0 °C, $PhICl_2$ (2.0 equiv.) was added. The reaction mixture was stirred for 5 min and cold pentane was added slowly to the solution. The mixture was kept in the freezer and 24 h later yellow crystals were obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 - 7.55 (m, 15H), 3.53 (s, 3H); ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 37.1;

Pentafluorophenyl(triphenylphosphine)gold(I) (16)[5]



To a mixture of pentafluorobenzene (0.50 mL, 4.5 mmol), silver(I)-oxide (174 mg, 0.75 mmol), potassium carbonate (242 mg, 1.75 mmol), pivalic acid (255 mg, 2.5 mmol) and triphenylphosphinegold(I) chloride (495 mg, 1.0 mmol), DMF (5 mL) was added. The reaction was heated at 50 °C for 4.5 h and the mixture was filtered through celite. The solvent was evaporated under reduced pressure. The crude was purified by column chromatography (hexane:CH_2Cl_2 1:1) to give 3 as a white solid. Yield: 86 % (538 mg, 0.86 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 - 7.43 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7 (ddsext, J = 226.0, 25.0, 4.0 Hz), 139.0 (dm, J = 246.0 Hz), 137.2 (t, J = 59.4 Hz), 137.2 (dm, J = 245.0 Hz), 134.3 (d, J = 14.1 Hz), 131.7 (d, J = 2.5 Hz), 129.8 (d, J = 55.4 Hz), 129.3 (d, J = 11.5 Hz); ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 43.13 (quint, J = 8.0 Hz); ^{19}F NMR (376 MHz, CD_2Cl_2): δ = -(116.33 - 116.65) (m), -159.29 (t, J = 19.8 Hz), -(162.80 -163.27) (m); MS (EI) m/z 626 (M+, 5). EI-HRMS Calcd. for $C_{24}H_{15}AuF_5P$: 626,0497, found: 626,0496.

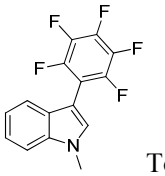
***cis*-Dichloro(pentafluorobenzene)(triphenylphosphine)gold(III) (17)**



To a mixture of pentafluorophenyl(triphenylphosphine)gold(I) (37.6 mg, 0.06 mmol) and iodobenzene-dichloride (18.1 mg, 0.066 mmol), carbon tetrachloride (3.8 mL) was added. The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure to ~0.2 mL and after addition of hexane the product precipitated. The product was separated on a filter paper to give **5** as a white solid. Yield: 93

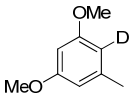
% (39.0 mg, 0.056 mmol). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.72 - 7.36 (m, 15H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ =143.7 (dm, J = 235.0 Hz), 140.4 (dm, J = 244.0 Hz), 138.0 (dm, J = 240.0 Hz), 134.9 (d, J = 10.7 Hz), 134.2 (d, J = 3.0 Hz), 129.8 (d, J = 12.5 Hz), 123.7 (d, J = 69.8 Hz); 31P NMR (162 MHz, CD2Cl2): δ = 35.64 (s); ^{19}F NMR (376 MHz, CD2Cl2): δ = -(123.48 - 124.35) (m), -156.90 (t, J = 19.8 Hz), -(159.92 - 160.91) (m); MS (EI) m/z 626 (M+ - Cl_2, 5).

1-methyl-3-(pentafluorophenyl)-indole (19)[6]



To a mixture of *cis*-chloro(dipentafluorophenyl)(triphenylphosphine)gold(III) (**17**) (4.1 mg, 0.005 mmol) and or 1- methylindole (0.015 mmol), 1,2-dichloroethane (0.63 mL) was added. The reaction was heated at 150 °C for 22 h. The solvent was evaporated under reduced pressure and the crude was purified by column chromatography (hexane:CH_2Cl_2 4:1) to give **19** as a white solid. Yield: 92 %. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 3.84 (s, 3H), 7.12 - 7.19 (m, 1H) 7.27 (td, J = 7.67, 1.04 Hz, 1H) 7.30 (s, 1H) 7.39 (d, J = 8.28 Hz, 1H) 7.42 - 7.49 (m, 1H). ^{19}F NMR (376 MHz, CD_2Cl_2): δ = -141.28 (dd, J = 23.2, 7.5 Hz), -159.22 (t, J = 20.7 Hz), -(163.81 - 164.07) (m); MS (EI) m/z 397 (M+, 100).

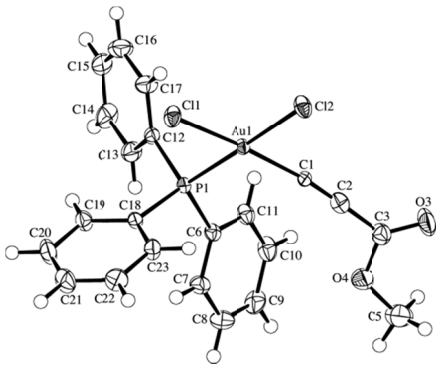
3,5-dimethoxy-1D-toluene (1b-d_1)



A solution of 2-bromo-3,5-dimethoxytoluene (500 mg, 2.16 mmol) in dry Et_2O (20 ml) at 0 °C was added via cannula to a solution of BuLi 2.5 M (1.4 ml, 3.45 mmol) in dry Et_2O (10 ml) at 0 °C. The resulting solution was warmed to room temperature and stirred for 2.5 h. Next, D_2O (2 mL) was slowly added and the resulting solution was stirred vigorously for 20 min. Then, the organic layer was separated and dried with $MgSO_4$ and the solvent was evaporated under reduce pressure. After column chromatography the product was obtained in 70% yield. ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 6.30-6.29 (m, 1H), 6.25-6.24 (m, 1H), 3.71 (s, 6H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 161.3, 140.7, 107.7, 98.2, 55.7, 22.3. MS (ESI) *m/z*: calcd for $C_9H_{11}DO_2$ (M+1): 154.0, found: 154.0. (> 90%D).

3.7 Crystallographic data

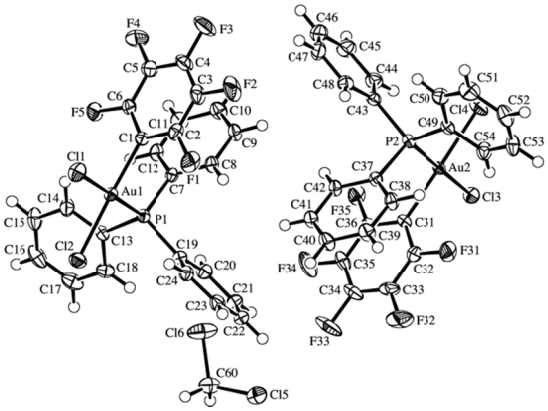
***cis*-Dichloro(triphenylphosphine)gold(III)acetylide (14)**



Crystallised from		dichloromethane / hexane
Empirical formula		$C_{22.5}H_{19}AuCl_3O_2P$
Formula weight [g mol^{-1}]		655.69
Crystal colour, habit		colorless, prism
Crystal dimensions [mm]		0.18 × 0.22 × 0.33
Temperature [K]		160(1)
Crystal system		monoclinic
Space group		$P2_1/n$ (#14)
Z		4
Reflections for cell determination		14109
2θ range for cell determination [°]		4–61
Unit cell parameters	a [Å]	12.59949(18)
	b [Å]	10.66900(13)
	c [Å]	17.9124(3)
	α [°]	90
	β [°]	108.3351(15)
	γ [°]	90
	V [Å^3]	2285.61(5)
F(000)		1260
D_x [g cm^{-3}]		1.905
μ(Mo $K\alpha$) [mm^{-1}]		6.896
Scan type		ω
2θ(max) [°]		60.9
Transmission factors (min; max)		0.552; 1.000
Total reflections measured		23037
Symmetry independent reflections		6250
R_{int}		0.033

Reflections with $I > 2\sigma(I)$	5692
Reflections used in refinement	6250
Parameters refined	282
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0239
$wR(F^2)$ (all data)	0.0536
Weights:	$w = [\sigma^2(F_o^2) + (0.0197P)^2 + 2.9702P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness of fit	1.052
Secondary extinction coefficient	0.00076(6)
Final Δ_{max}/σ	0.004
$\Delta\rho$ (max; min) [e Å^{-3}]	1.24; -1.19
$\sigma(d_{(C-C)})$ [Å]	0.004 – 0.005

cis-Dichloro(pentafluorophenyl)(triphenylphosphine)gold(III)(17)



Crystallised from	hexane / CH_2Cl_2
Empirical formula	$C_{24.5}H_{16}AuCl_3F_5P$
Formula weight [g mol^{-1}]	739.69
Crystal colour, habit	colourless, prism
Crystal dimensions [mm]	0.10 × 0.13 × 0.26
Temperature [K]	160(1)
Crystal system	monoclinic
Space group	$P2_1/c$ (#14)
Z	8
Reflections for cell determination	28805
2θ range for cell determination [°]	4–61
Unit cell parameters a [Å]	12.02057(14)
b [Å]	26.0858(3)
c [Å]	15.64560(17)

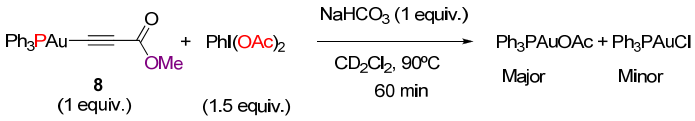
α [°]	90
β [°]	93.8309(10)
γ [°]	90
V [Å^3]	4894.98(9)
Probability for the ellipsoid plots [%]	50

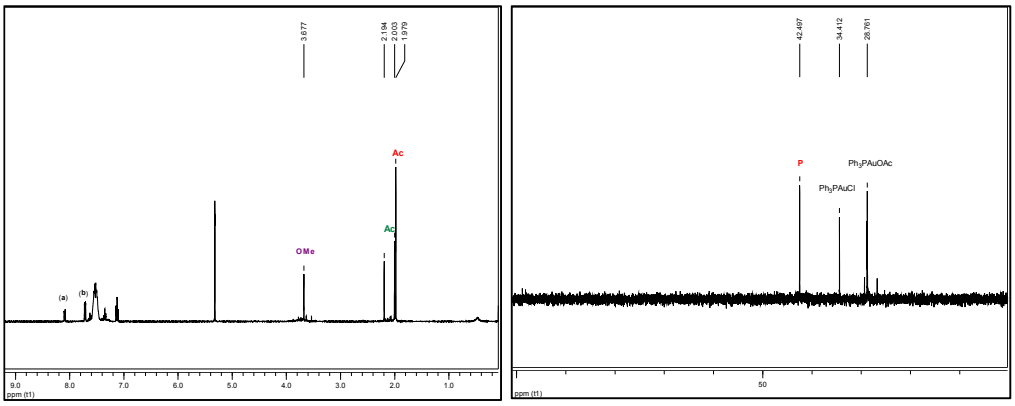
3.8 Supplementary data

3.8.1 ^{31}P and ^{1}H NMR spectroscopic datas for the stoichiometric studies

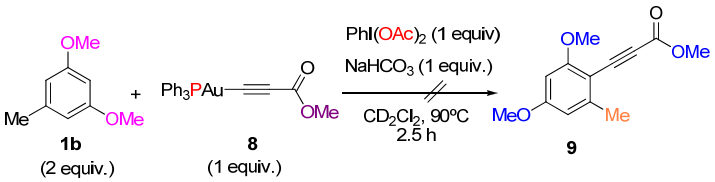
Stoichiometric experiments using gold(I) acetylide **8**

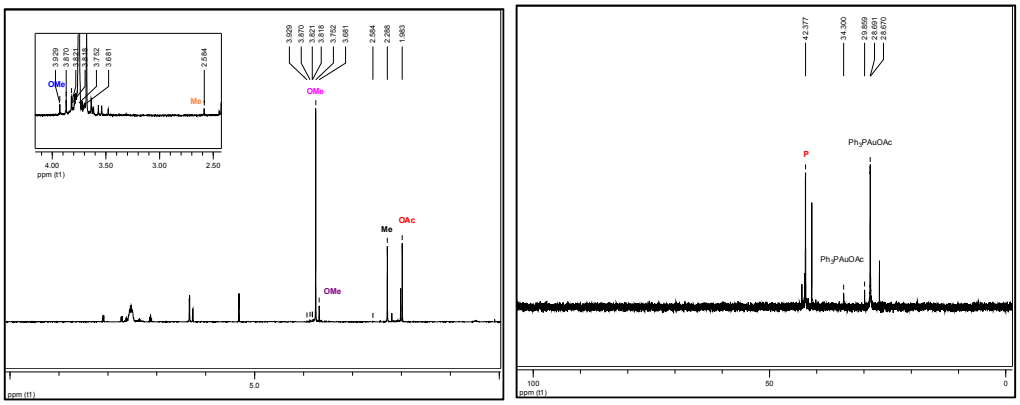
- Oxidation of gold(I) acetylide **8** with $PhI(OAc)_2$ (eq. 5 in the aticle)



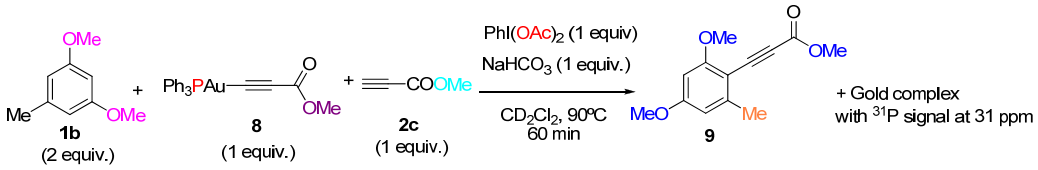


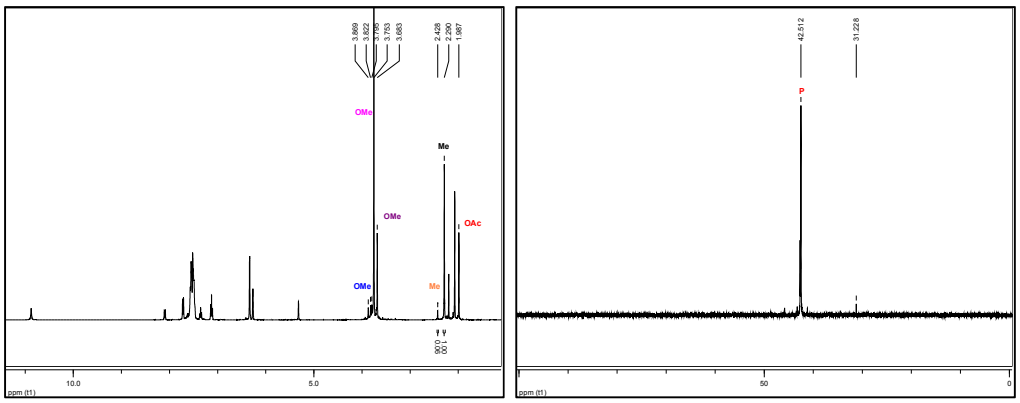
- Ethynylation of 3,5-dimethoxytoluene (**1b**) with stoichiometric gold(I)acetylide **8** (eq. 6 in the aticle)



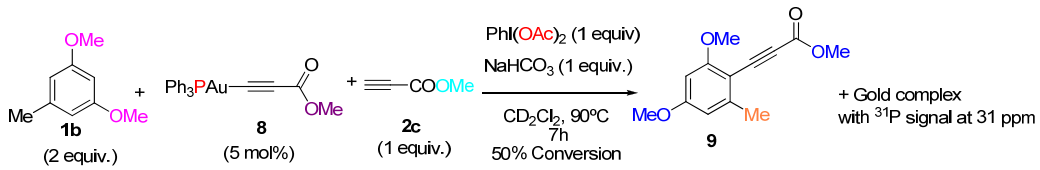


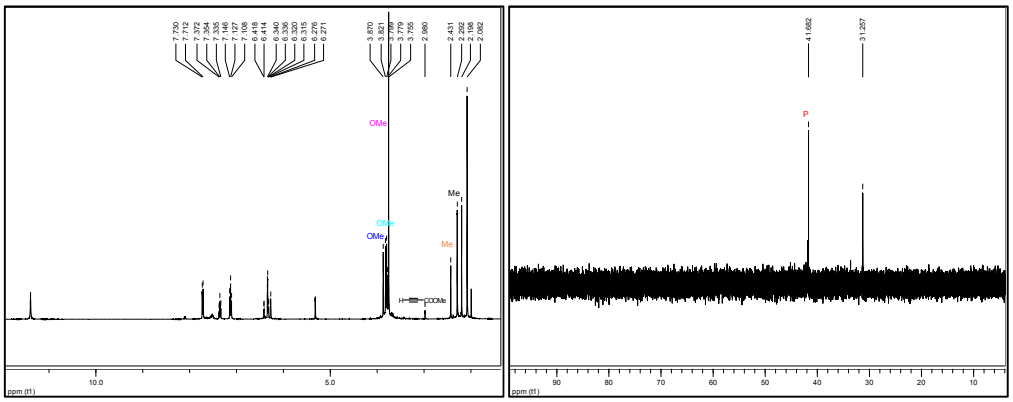
- Ethynylation of 3,5-dimethoxytoluene **1b** with stoichiometric amount of **8** and free methyl propiolate **2c** (eq. 7 in the article)



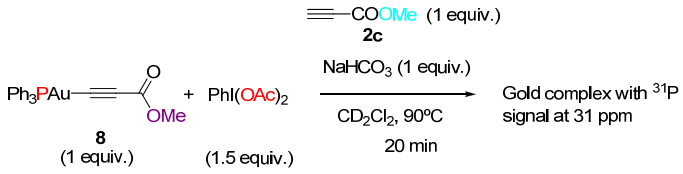


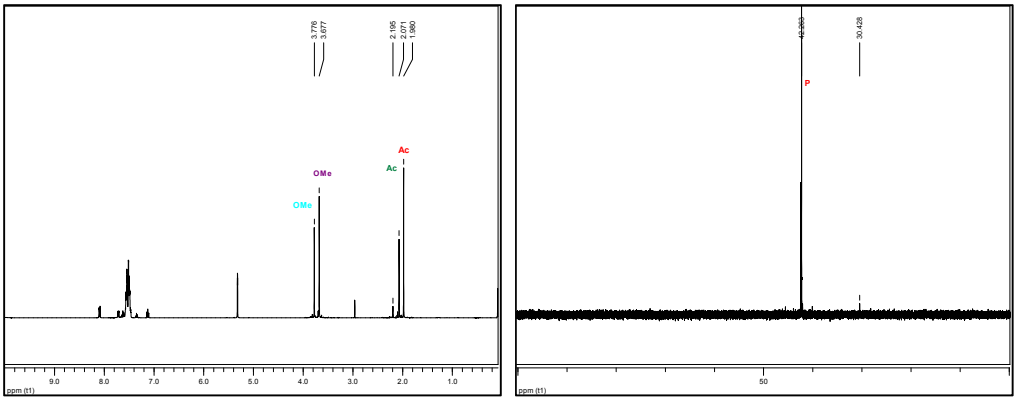
- Ethynylation of 3,5-dimethoxytoluene **1b** with 5 mol% of **8** and free methyl propiolate **2c** (eq. 8 in the article)



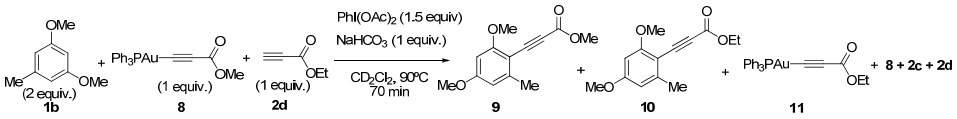


- Oxidation of gold(I) acetylide **8** with $PhI(OAc)_2$ with free methyl propiolate 2c (eq. 9 in the article)

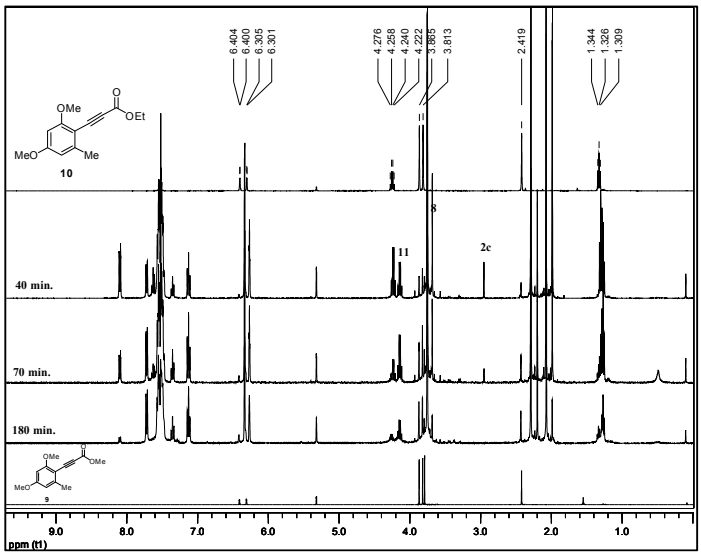




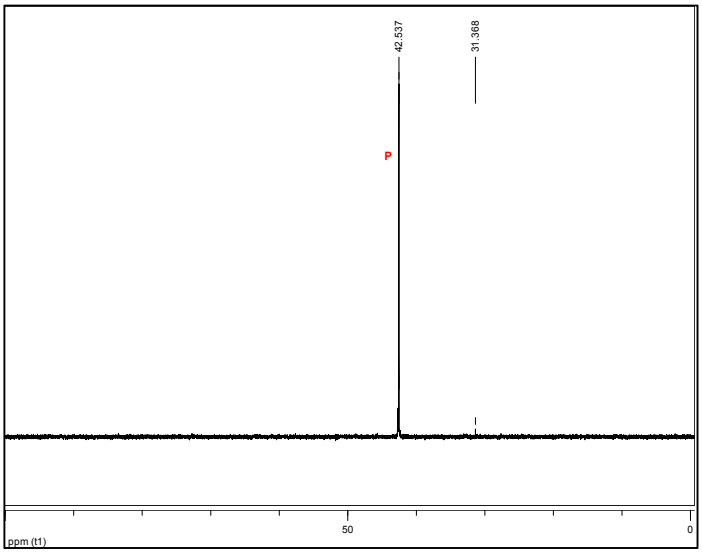
- Ethynylation of 3,5-dimethoxytoluene **1b** with stoichiometric amount of **8** and free ethyl propiolate **2d** (eq. 10 in the article)



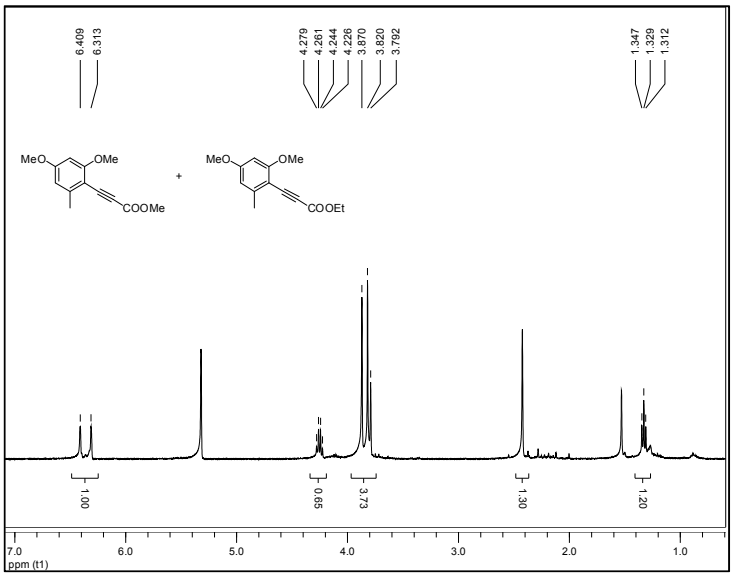
Following the reaction by ^{1}H NMR:



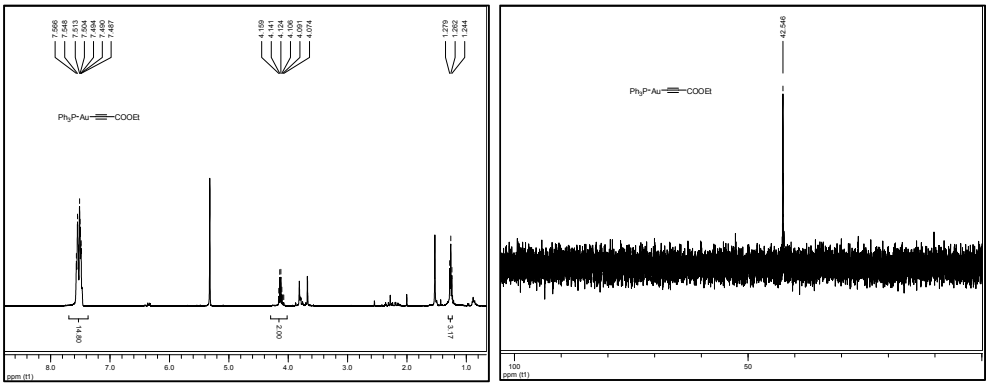
^{31}P NMR of the reaction mixture



Pure mixture of products **9** and **10** in a ratio 1:1

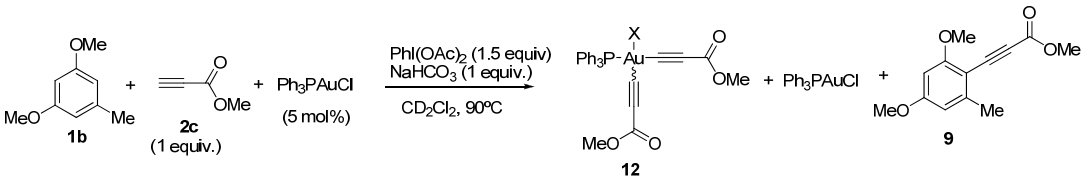


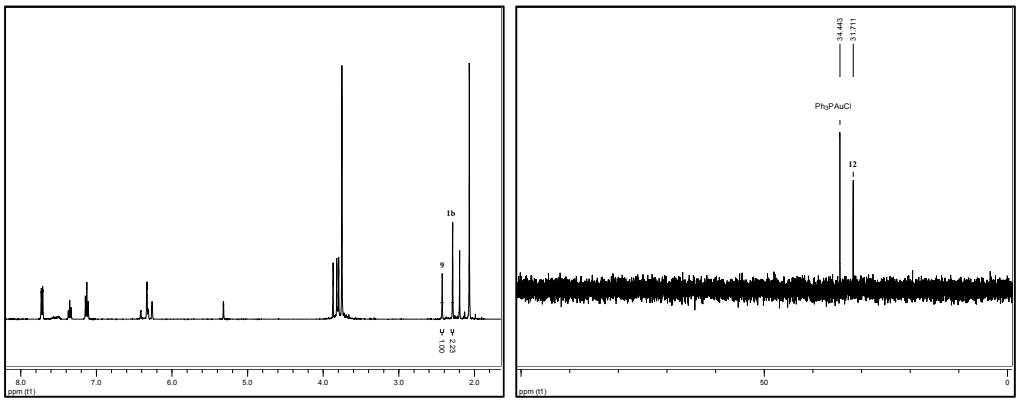
Characterization of gold(I)-acetylide **11**.



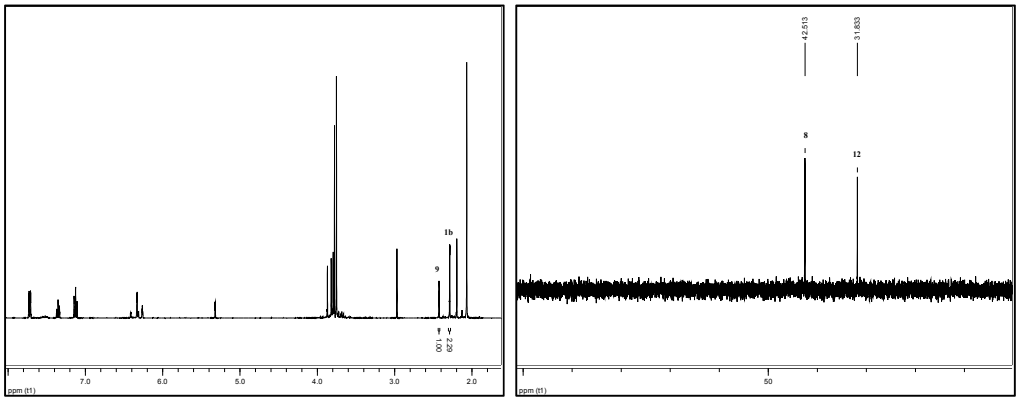
Is the gold complex with a ^{31}P signal at 31 ppm the active specie of the catalytic cycle?

- Experiment which showed that the gold complex at 31 ppm is the resting state of the catalyst (Scheme 5 in the article)

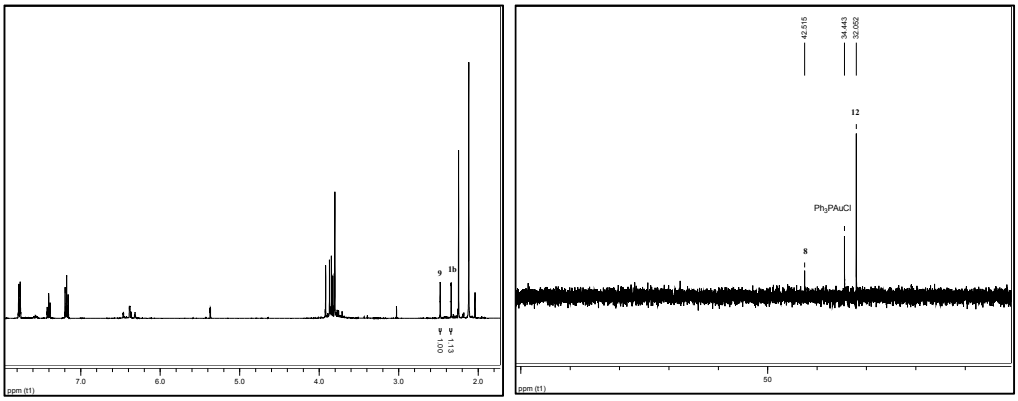




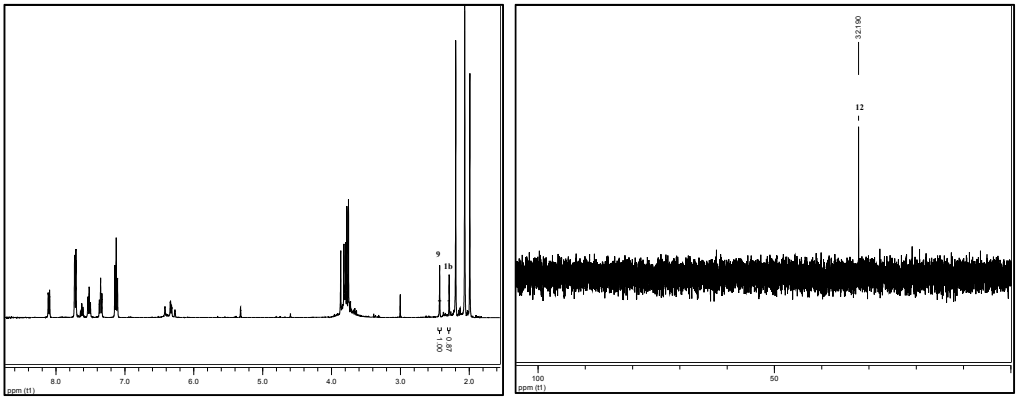
1 equiv. of methyl propiolate **2c** was added to this mixture and the reaction was heated at 90 °C. After 60 min. the Ph_3PAuCl was transformed into the gold(I)-acetylide **8** without obtaining more conversion to the product.



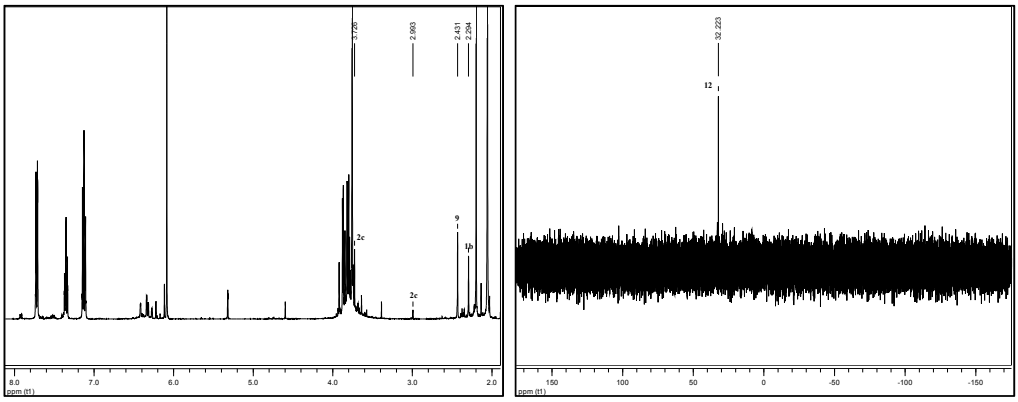
1.5 equiv. of $PhI(OAc)_2$ was then added to the reaction mixture. After 10 h only traces of the gold acetylide **8** and Ph_3PAuCl were detected in the reaction mixture. Furthermore, major conversion to the product was observed.



Several additions of methyl propiolate **2c** and oxidant afforded the complex **12** as the single gold specie in the reaction mixture.



To this solution 1 equiv. of 1,3,5-trimetoxy benzene **1a** was added. After heating at 90 °C for 6 h only traces of 2,4,6-trimetoxyiodobenzene was observed, indicating that the gold complex at 31 ppm in ^{31}P NMR is the dead-end of the catalytic system.

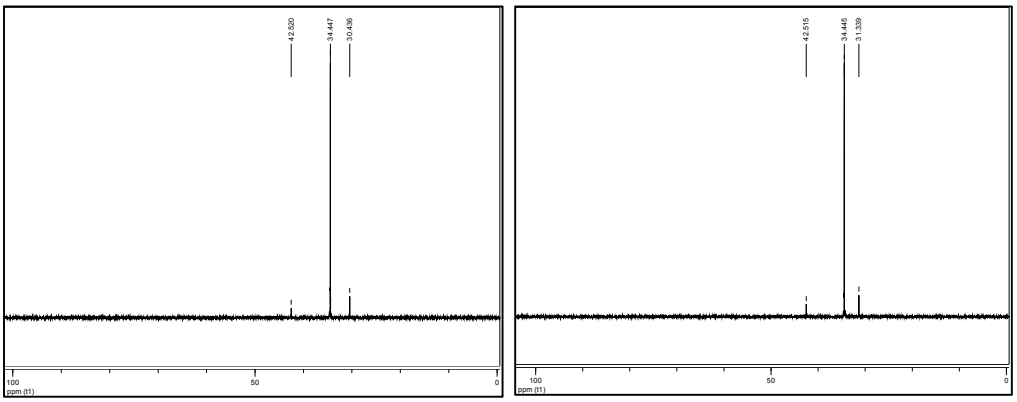


Effect of the AcOH (Ref. 30 in the article)

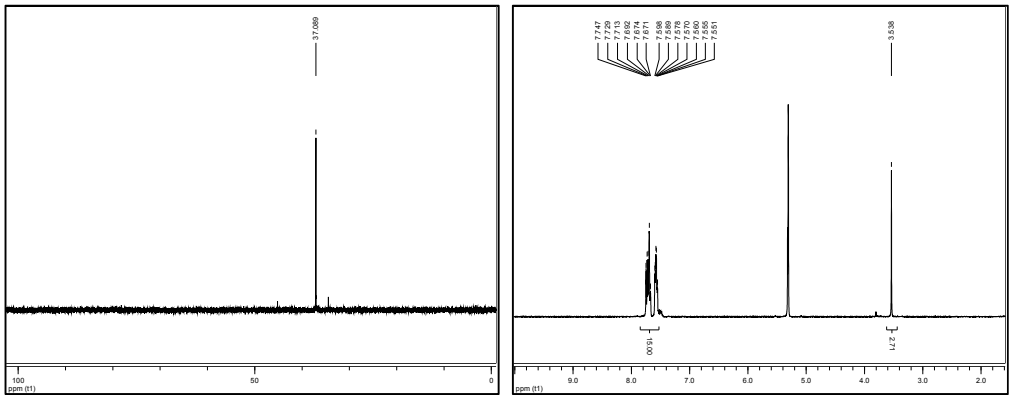
The peak at 31 ppm is shifted from 30.4 to 32.3 ppm during the reactions due to the increase of concentration of acetic acid in the solution. This hypothesis was confirmed when just upon

addition of AcOH (0.7 equiv) to a reaction containing the gold complex with the peak at 30.4 ppm was shifted to 31.3 ppm.

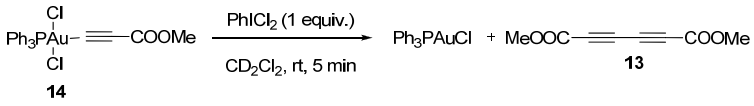
Before addition of AcOH After addition of 0.7 equiv. AcOH

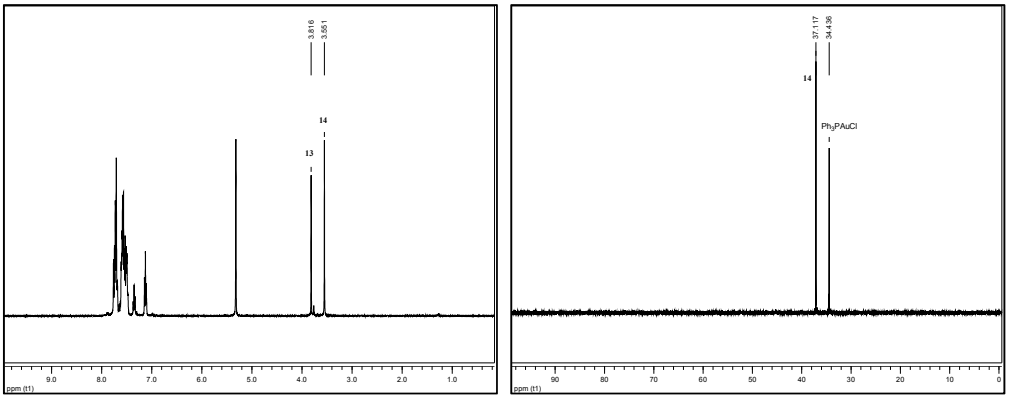


- Characterization of dichloro-gold(III)-acetylide **14** (^{1}H and ^{31}P NMR) (Scheme 6 in the article)

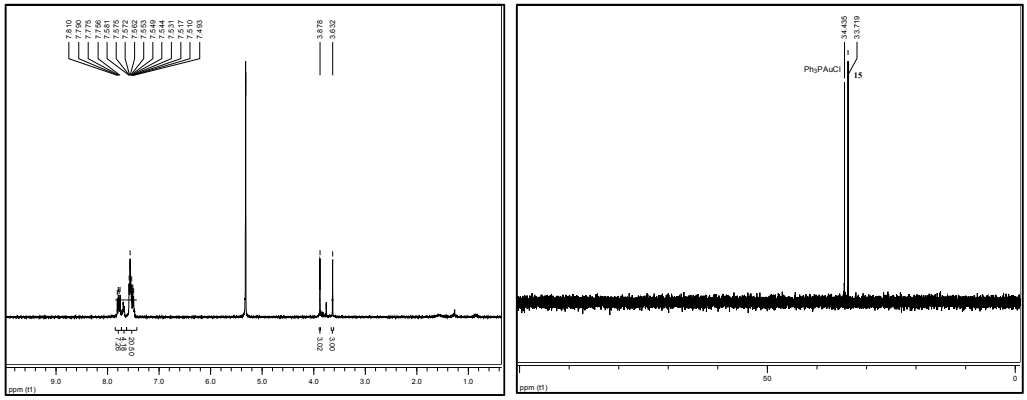


Reaction of gold(I)-acetylide **8** with 1 equiv. of $PhICl_2$ (Scheme 7 in the article)



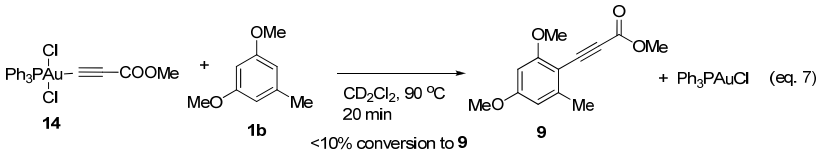


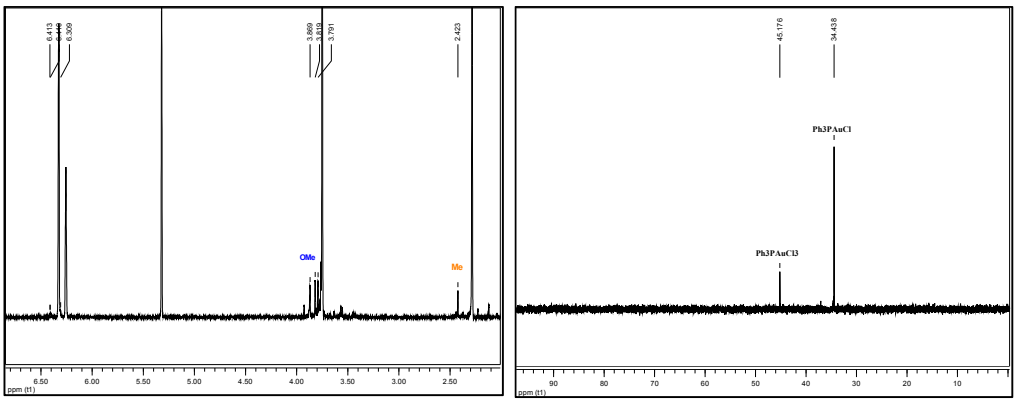
^{1}H and ^{31}P NMR of the possible gold(III)-bisacetylide **15** with Ph_3PAuCl (Ref. 35 in the article)



The synthesis of gold(III)-bisacetylide **15** by ligand exchange in dichlorogold(III)-acetylide with the silver or the sodium salt of methyl propiolate was not success, a mixture of products were obtained in both cases.

Reaction of gold(III)-acetylide **14** with 2 equiv. of 3,5-dimethoxytoluene **1b** (eq. 12 in the article)





3.8.2 Kinetic Studies

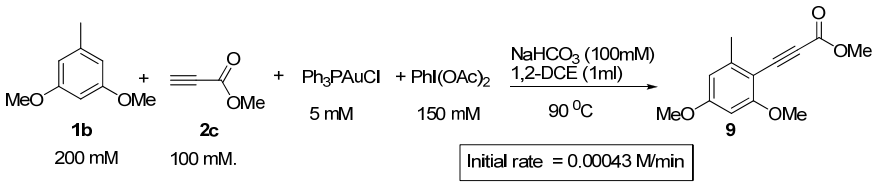
3.8.2.1 General procedure for kinetic experiments

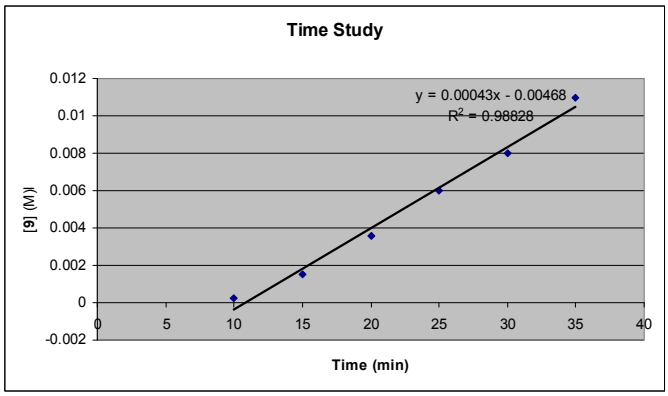
Kinetic experiments were run in sealed tubes with Teflon-lined caps, and each data point within a kinetics run represents a reaction in an individual sealed tube, with each vial containing a constant concentration of oxidant, catalyst, $NaHCO_3$, arene and alkyne.

Representative example: $NaHCO_3$ (0.1 mmol, 8.4 mg) was weight into each sealed tube, then 1 ml of a standard solution containing (per aliquot) 3,5-dimetoxytoluene (**1b**) (0.2 mmol, 29.3 µl), methyl propiolate (**2c**) (0.1 mmol, 9 µl), $PhI(OAc)_2$ (0.15 mmol, 48.3 mg), Ph_3PAuCl (0.005 mmol, 2.5 mg) and dodecane as the internal standard (0.05 mmol, 11.3 µl) in 1,2-dichloroethane. The reactions were heated at 90 °C for different times. The reaction was quenched by cooling the vial to 0 °C in an ice bath. Once the reaction is cold, 0.1 ml of the solution is filtered by a pad of Celite and the Celite was washed with 0.9 ml of DCE. Then, 2 µl of this sample is injected in the GC. The reaction was analyzed by GC and the yield of the product aryl alkyne **9** for each time point was determined versus internal standard dodecane. Importantly we confirmed that the reaction did not progress after the quench. For example, an identical GC yield was obtained for a reaction analyzed immediately versus one analyzed after 6 h. Furthermore, it was also confirmed by NMR spectroscopy. A reaction mixture store in the fridge for 48 h had the same conversion to the product than after the quenching.

The initial rate under each set of reaction conditions was obtained using the initial rates method. Each of the reaction was run to < 20% conversion (as determined by GC analysis) and the concentration of the product [**9**] was plotted versus reaction time. A straight line was fitted to this plot (generally $R^2 > 0.96$). An example of the initial rate determination is shown in Scheme 17.

Scheme 17. Representative kinetic experiment





Order in the 3,5-dimethoxytoluene (**1b**): The order in the arene **1b** was determined by studying the initial rate of reactions with different [**1b**]. The general procedure mention above was used. $NaHCO_3$ (0.1 mmol, 8.4 mg) was weight into each sealed tube, then 1 ml of a

standard solution containing (per aliquot) 3,5-dimethoxytoluene (**1b**) (0.1-0.25 mmol, 14.6-36.5 µl) methyl propiolate (**2c**) (0.1 mmol, 9 µl), $PhI(OAc)_2$ (0.15 mmol, 48.3 mg), Ph_3PAuCl (0.005 mmol, 2.5 mg) and dodecane as the internal standard (0.05 mmol, 11.3 µl) in 1,2-dichloroethane. Reaction were heated at 90 °C and quenched by cooling the vial to 0 °C in an ice bath. Once the reaction is cold, 0.1 ml of the solution is filtered by a pad of Celite and the Celite was washed with 0.9 ml of DCE. Then, 2µl of this sample is injected in the GC. The yield of product for each time point was determined versus internal standard dodecane. A plot of initial rate (Δ[**9**]/Δt) versus [**1b**] (Scheme 9) shown no dependence on the concentration of arene.

Order in the methyl propiolate (**2c**): The order in the alkyne **2c** was determined by studying the initial rate of reactions with different [**2c**]. The general procedure mention above was used. $NaHCO_3$ (0.1 mmol, 8.4 mg) was weight into each sealed tube, then 1 ml of a standard solution containing (per aliquot) methyl propiolate (**2c**) (0.05-0.2 mmol, 4.6-18 µl), 3,5-dimetoxytoluene (**1b**) (0.2 mmol, 29.3 µl), $PhI(OAc)_2$ (0.15 mmol, 48.3 mg), Ph_3PAuCl (0.005 mmol, 2.5 mg) and dodecane as the internal standard (0.05 mmol, 11.3 µl) in 1,2-dichloroethane. Reaction were heated at 90 °C and quenched by cooling the vial to 0 °C in an ice bath. Once the reaction is cold, 0.1 ml of the solution is filtered by a pad of Celite and the Celite was washed with 0.9 ml of DCE. Then, 2µl of this sample is injected in the GC. The yield of product for each time point was determined versus internal standard dodecane on the basis of average of 3 successive GC analyses of the same sample. Each reported initial rate represents an average of two unique kinetic experiments. A plot of initial rate (Δ[**9**]/Δt) versus [**2c**] (Scheme 10) gave a straight line ($R^2 = 0.9968$), indicative of a 1st order dependence on [**2c**].

Order in the oxidant: The order in the $PhI(OAc)_2$ was determined by studying the initial rate of reactions with different [$PhI(OAc)_2$]. The general procedure mention above was used. $NaHCO_3$ (0.1 mmol, 8.4 mg) was weight into each sealed tube, then 1 ml of a standard solution containing (per aliquot) 3,5-dimethoxytoluene (**1b**) (0.2 mmol, 29.3 µl) methyl propiolate (**2c**) (0.1 mmol, 9 µl), $PhI(OAc)_2$ (0.05-0.175 mmol, 16.1-56.4 mg), Ph_3PAuCl (0.005 mmol, 2.5 mg) and dodecane as the internal standard (0.05 mmol, 11.3 µl) in 1,2-dichloroethane. Reaction were heated at 90 °C and quenched by cooling the vial to 0 °C in an ice bath. Once the reaction is cold, 0.1 ml of the solution is filtered by a pad of Celite and the Celite was washed with 0.9 ml of DCE. Then, 2µl of this sample is injected in the GC. The yield of product for each time point was determined versus internal standard dodecane. A plot of initial rate (Δ[**9**]/Δt) versus [oxidant] (Scheme 11) gave a straight line ($R^2 = 0.9943$), indicative of a 1st order dependence on the oxidant

Order in the Catalyst: The order in the catalyst was determined by studying the initial rate of reactions with different [Ph_3PAuCl]. The general procedure mention above was used. $NaHCO_3$ (0.1 mmol, 8.4 mg) was weight into each sealed tube, then 1 ml of a standard solution containing (per aliquot) 3,5-dimethoxytoluene (**1b**) (0.2 mmol, 29.3 µl) methyl propiolate (**2c**) (0.1 mmol, 9 µl), $PhI(OAc)_2$ (0.15 mmol, 48.3 mg), Ph_3PAuCl (0.002-0.008 mmol, 1-4 mg) and dodecane as the internal standard (0.05 mmol, 11.3 µl) in 1,2-dichloroethane. Reaction were heated at 90 °C and quenched by cooling the vial to 0 °C in an ice bath. Once the reaction is cold, 0.1 ml of the solution is filtered by a pad of Celite and the celite was washed with 0.9 ml of DCE. Then, 2µl of this sample is injected in the GC. The yield of product for each time point was determined versus internal standard dodecane. A plot of initial rate (Δ[**9**]/Δt) versus [Ph_3PAuCl] (Scheme 12) gave a straight line (R^2 = 0.9955), indicative of a 1st order dependence on the catalyst.

Order in the AcOH: The conditions used were as follows: $NaHCO_3$ (0.1 mmol, 8.4 mg) was weight into each sealed tube, then 1 ml of a standard solution containing (per aliquot) 3,5-dimetoxytoluene (**1b**) (0.2 mmol, 29.3 µl), methyl propiolate (**2c**) (0.1 mmol, 9 µl), $PhI(OAc)_2$ (0.15 mmol, 48.3 mg), Ph_3PAuCl (0.005 mmol, 2.5 mg), AcOH (0.01-0.04 mmol, 0.6-2.3 µl) and dodecane as the internal standard (0.05 mmol, 11.3 µl) in 1,2-dichloroethane. Reaction were heated at 90 °C and quenched by cooling the vial to 0 °C in an ice bath. Once the reaction is cold, 0.1 ml of the solution is filtered by a pad of Celite and the Celite was washed with 0.9 ml of DCE. Then, 2µl of this sample is injected in the GC. The yield of product for each time point was determined versus internal standard dodecane. A plot of initial rate (Δ[**9**]/Δt) versus $[AcOH]^{-1}$ (Scheme 12) gave a straight line (R^2 =0.9935), indicative of a inverse 1st order dependence on the catalyst.

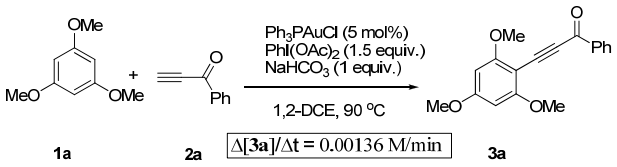
3.8.2.2 Kinetic isotopic effect

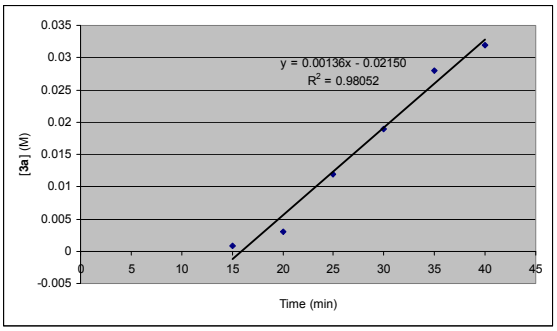
Intermolecular Kinetic isotopic effect for Ar-H activation

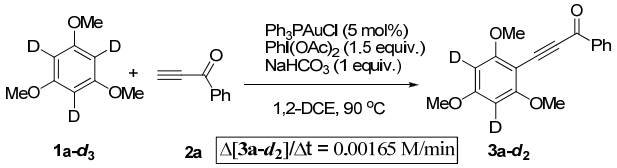
The intermolecular kinetic isotope effect was determined by studying the initial rate of the reactions with 1,3,5-trimethoxybenzene (**1a**) and the corresponding deuterated arene **1a-*d*$_3$**[7]. The general procedure mention above was used. $NaHCO_3$ (0.1 mmol, 8.4 mg) was weight into each sealed tube, then 1 ml of a standard solution containing (per aliquot) 1,3,5-trimethoxybenzene (**1a**) (0.2 mmol, 33.6 mg) or deuterated arene **1a-*d*$_3$** (0.2 mmol, 34 mg), phenyl acetylene (**2a**) (0.1 mmol, 11 µl), $PhI(OAc)_2$ (0.15 mmol, 48.3 mg), Ph_3PAuCl (0.005 mmol, 2.5 mg) and dodecane as the internal standard (0.05 mmol, 11.3 µl) in 1,2-dichloroethane. The reactions were heated at 90 °C for different times. The reaction were quenched by cooling the vial to 0 °C in an ice bath, Once the reaction is cold, 0.1 ml of the solution is filtered by a pad of Celite and the Celite was washed with 0.9 ml of DCE. Then,

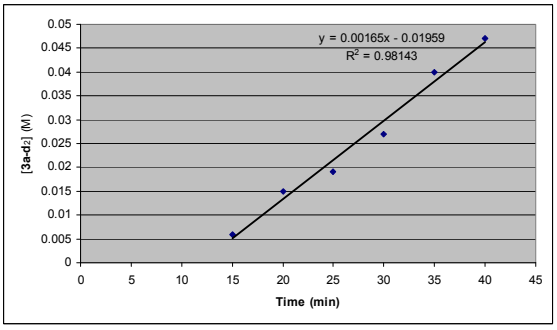
2µl of this sample is injected in the GC. The reaction was analyzed by GC and the yield of the aryl alkyne **3a** or **3a-*d*$_2$** at each time point was determined versus internal standard dodecane (Scheme 18).

Scheme 18. Intermolecular Kinetic isotopic effect for Ar-H activation







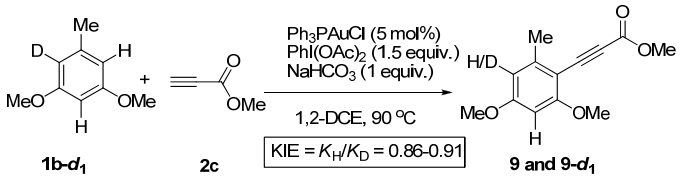


Intramolecular Kinetic isotopic effect for Ar-H activation

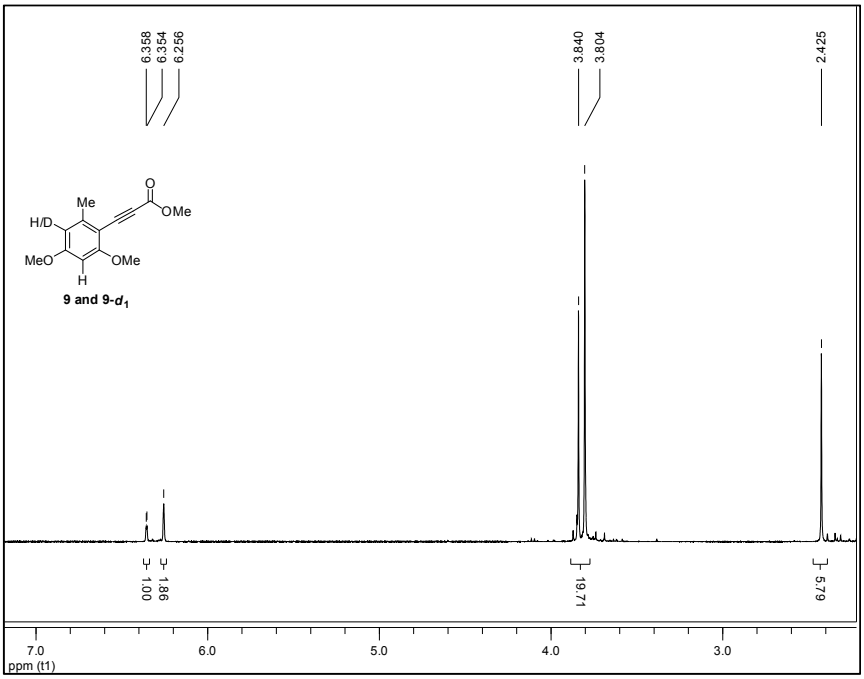
The intramolecular kinetic isotope effect was obtained using substrate **1b-*d*$_1$** (0.2 mmol, 29.5 µl), methyl propiolate (**2c**) (0.1 mmol, 9 µl), PhI(OAc)$_2$ (0.15 mmol, 48.3 mg), Ph$_3$PAuCl (0.005 mmol, 2.5 mg) in 1,2-dichloroethane (1 ml). The reaction was heated at 90 °C for 24 h. The solvent of the reaction mixture was evaporated and the product was isolated by column chromatography on silica gel. The isotope effect was determined by comparison of the integration of the signal at 6.36 ppm corresponding to 1H from **9** relative to the singlet at 6.26 ppm which contains 1H from **9-*d*$_1$** and 1H from **9** (Scheme 19). In addition, the reaction crude

was analyzed by MS. (Area $C_{13}H_{14}NaO_4$ = 1513313, Area $C_{13}H_{13}DNaO_4$ = 1639943). Based on NMR of the purified mixture shown KIE = 0.86 whereas MS spectroscopy analysis of the reaction mixture shown a KIE = K_H/K_D = 0.91.

Scheme 19. Intramolecular Kinetic isotopic effect for Ar-H activation



^{1}H NMR (400 MHz, $CDCl_3$)

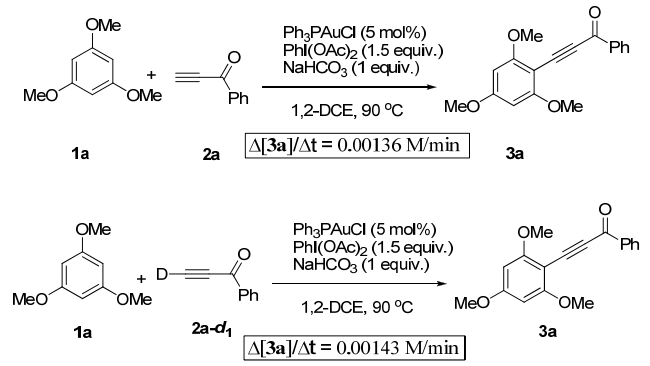


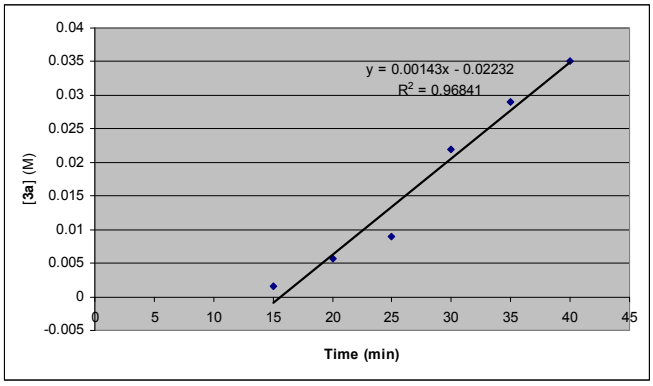
Intermolecular Kinetic isotopic effect for Csp-H activation

The intermolecular kinetic isotope effect was determined by studying the initial rate of reactions with phenyl acetylene (**2a**) and the corresponding deuterated alkyne **2a-*d*$_1$**[8]. The general procedure mention above was used. $NaHCO_3$ (0.1 mmol, 8.4 mg) was weight into each sealed tube, then 1 ml of a standard solution containing (per aliquot) 1,3,5-trimethoxybenzene (**1a**) (0.2 mmol, 33.6 mg) phenyl acetylene (**2a**) (0.1 mmol, 11 µl) or *d*$_1$-phenylacetylene (**2a-*d*$_1$**) (0.1 mmol, 11.3 µl), $PhI(OAc)_2$ (0.15 mmol, 48.3 mg), Ph_3PAuCl (0.005 mmol, 2.5 mg) and dodecane as the internal standard (0.05 mmol, 11.3 µl) in 1,2-dichloroethane. The reactions were heated at 90 °C for various amount of time. The reaction were quenched by cooling the vial to 0 °C in an ice bath, Once the reaction is cold, 0.1 ml of the solution is filtered by a pad of Celite and the Celite was washed with 0.9 ml of DCE.

Then, 2µl of this sample is injected in the GC. The reaction was analyzed by GC and the yield of the aryl alkyne **3a** at each time point was determined versus internal standard dodecane (Scheme 19).

Scheme 20. Intermolecular Kinetic isotopic effect for Csp-H activation





3.9 References

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Chapter 4

Flexible Gold-Catalyzed Regioselective Oxidative Difunctionalization of Unactivated Alkenes

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Flexible Gold-Catalyzed Regioselective Oxidative Difunctionalization of Unactivated Alkenes

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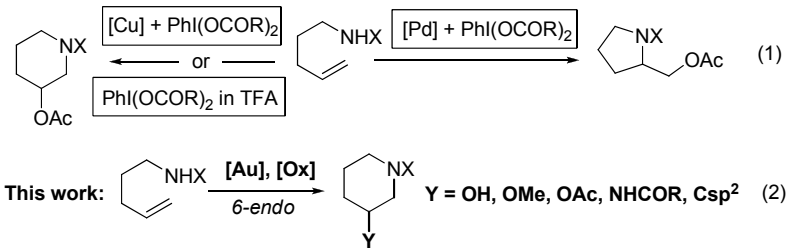
(*Angew. Chem. Int. Ed.* **2011**, *50*, 906)

Diols, diamines and aminoalcohols are ubiquitous functionalities in complex organic molecules. From the seminal work from Sharpless and co-workers on the intermolecular osmium-catalyzed asymmetric dihydroxylation and aminohydroxylation of alkenes,[1] the development of alternative methods to access these privileged motifs has become a priority for synthetic organic chemists. In recent years, palladium catalysts in combination with $PhI(OAc)_2$ as oxidant have been successfully used in the aminooxygenation and diamination of unactivated alkenes both intra-[2] and intermolecularly.[3] These transformations rely on the oxidation of Pd(II) to Pd(IV) species to facilitate the C-X bond formation.[4,5] Copper[6] and also metal-free[7] reactions have been reported although the required acidic media in the later processes might limit its potential application in more elaborated settings (Scheme 1, eq. 1). Our group has recently combined the unique carbophilicity of gold complexes with gold(I)/gold(III) redox catalytic cycles to design new transformations.[8,9] Surprisingly though, only one example of gold catalyzed oxidative diamination of alkenes from ureas has been reported up to date.[10] We envisioned that highly oxidized gold(III) intermediates generated in the presence of oxidants such as Selectfluor or $PhI(OAc)_2$ could trigger the selective oxidative difunctionalization of alkenes (Scheme 1, eq. 2).

Scheme 1. Intramolecular oxidative difunctionalization of alkenes

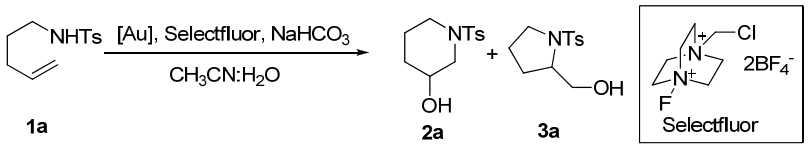


Herein we report the successful realization of this concept in a flexible alkene aminooxygenation reaction which allows the introduction of alcohols, ethers or esters into the

hydroamination products. We also present a novel aminoamidation process through an in situ gold-activation of nitriles and an intramolecular oxidative arylation to access cumbered tricyclic benzazepine scaffolds, all based on gold(I)/gold(III) catalytic cycles.

Our study commenced with *N*-tosyl-4-pentenyl amine (**1a**) as substrate using Selectfluor as stoichiometric oxidant (Table 1).[11]

Table 1. Optimization of the Au-catalyzed aminohydroxylation



1a **2a** **3a**

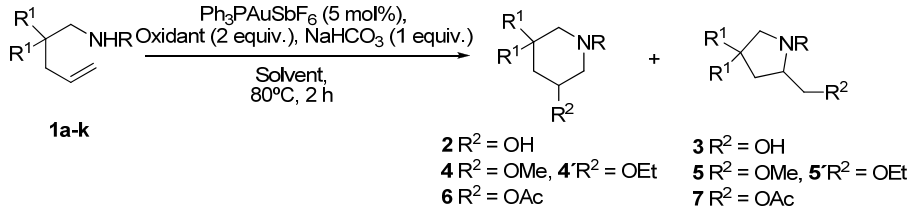
Entry	Modification of the standard conditions[a]	Conv.[b] (%)	**2a**:**3a** ratio, (Yield, %)
1	No gold, 12 h	0	-
2	Ph_3PAuCl, 12 h	0	-
3	**$Ph_3PAuSbF_6$, 2 h**	**100**	**9:1 (78)**
4	As entry 3, no base	70	n.d. [c]
5	$Ph_3PAuNTf_2$, 2 h	100	9:1
6	$IPrAuNTf_2$, 12 h	0	-
7	$[(2,4\text{-di-}t\text{Bu}C_6H_3O)_3P]AuSbF_6$, 12 h	0	-
8	$(PhO)_3PAuSbF_6$, 12 h	50	4:1

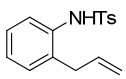
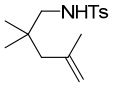
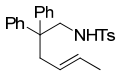
[a] Standard conditions: [Au]: 5 mol %, Selectfluor (2 equiv.), $NaHCO_3$ (1.1 equiv.), $CH_3CN:H_2O$ (20:1), 0.02 M, 80ºC. [b] Checked by ^{1}H-NMR. [c] n.d.: not determined

The reaction in the absence of gold or with neutral Ph_3PAuCl returned the starting material (Table 1, entries 1 and 2). Using a cationic $Ph_3PAuSbF_6$ complex, we were pleased to observe complete conversion of the starting material into aminoalcohols **2a**, and **3a**. The reaction was highly regioselective favouring the 6-*endo*-cyclization product in a 9:1 ratio (Table 1, entry 3). In the absence of base, the reaction proved to be more sluggish (Table 1, entry 4). The counteranion in the gold complex did not influence the reaction outcome as shown in entry 5. In contrast, the size and electronic nature of the ligand bound to gold seemed to play an important role. Thus, the use of a bulky *N*-heterocyclic ligand such as 1,3-bis(2,6-diiso-propylphenyl)-imidazol-2-ylide or a more electrophilic tris-(2,4-di-*tert*butylphenyl)phosphite ligand completely inhibited the reaction (Table 1, entries 6 and 7). A less bulky triphenylphosphite not only slowed down the reaction but also affected the regioselectivity of the process as compared to entry 3 (Table 1, entry 8). Remarkably, under the optimized conditions (Table 1, entry 3), potentially competitive processes such as protodemetallation to give 1-tosylpiperidine or *β*-hydrogen elimination to give 1-tosyl-1,2,3,4-tetrahydropyridine

were never detected. We then set out to explore the scope of this *endo*-selective gold-catalyzed aminohydroxylation reaction (Table 2).

Table 2. Scope of the gold-catalyzed aminooxygenation reaction



Entry	React. Cond. [a]	Substrate, R, R^1	Products (Ratio)[b]	Yield, (%)[c]
1	A	**1a**: R = Ts, R^1 = H	**2a**:**3a** (9:1)	78[d]
2	A	**1b**: R = Ts, R^1 = Ph	**2b**:**3b** (9:1)	85
3	B	"	**4b**:**5b** (9:1)	87
4	C	"	**6b**:**7b** (4:1)	76
5	A	**1c**: R = Ts, R^1 = Me	**2c**	85
6	B´	„	**4c´**	77
7	C	"	**6c**	80
8	A	**1d**: R = Ts, R^1 = -$(CH_2)_5$-	**2d**	80
9	A	**1e**: 	**2e**:**3e** (1.5:1)	50[d]
10	A	**1f**: R = Ms, R^1 = Me	**2f**	80[e]
11	A	**1g**: R = Mesitylsulfonyl, R^1 = Me	**2g**	77[e]
12	A	**1h**: R = *o*-NO_2-C_6H_4, R^1 = Me	**-**	-
13	A	**1i**: R = Cbz, R^1 = Me	**2i**:**3i´´**(1:2)	82[13]
14	C	**1j**: 	**2j**	79
15	A, B	**1k**: 	**-**	-

[a] Conditions A: Same as Table 1, entry 3; Cond. B: Selectfluor (2 equiv.), CH_3CN:MeOH (20:1), 0.02 M; Cond. B´: as B but with EtOH; Cond. C: $PhI(OAc)_2$ (2 equiv.), 1,2-DCE, 0.1 M, 12 h. [b] Determined by ^{1}H-NMR in the crude reaction mixture. [c] Isolated yield for major regioisomer. [d] Yield of the mixture. [e] Reaction time: 12 h

First we examined the effect of substituents in the backbone of the aminopentene substrates. *N*-Tosyl-(2,2-diphenylpent-4-enyl) amine (**1b**) reacted efficiently under the optimized conditions to give 1,3-amino alcohol **2b** in 85% yield (Table 2, entry 2).[12] When the reaction was performed in a mixture CH_3CN:MeOH, the corresponding aminomethoxylated product

4b could be obtained in 87% yield (Table 2, entry 3).[2e] Switching to $PhI(OAc)_2$ as stoichiometric oxidant in 1,2-dichloroethane as solvent, the corresponding aminoacetoxylation product **6b** was obtained in 76% yield, although lower regioselectivity was detected still favouring the piperidine product (4:1) (Table 2, entry 4).

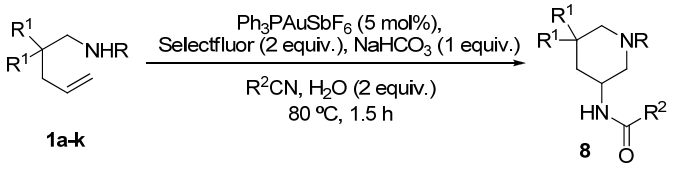
These results highlight the synthetic utility of this gold catalyzed process, since 1,3-aminoalcohols, ethers or acetates can be selectively obtained in a highly efficient manner through slight modifications of the reaction conditions. 2,2-Dimethyl and 2-cyclohexyl-substituted substrates **1c-d** afforded 1,3-aminoalcohols **2c-d** in 85 and 80% yield respectively as single regioisomers under the standard conditions (Table 2, entries 5 and 8). The reaction of **1c** in the presence of EtOH afforded **4c´** in 77% yield whereas with $PhI(OAc)_2$ as oxidant aminoacetate **6c** was isolated in 80% yield (Table 2, entries 6 and 7). In the case of aniline **1e**, an unseparable 1.5:1 mixture of *6-endo* and *5-exo* aminohydroxylation products **2e** and **3e** was obtained in 50% yield (Table 2, entry 9). We then evaluated the influence of the *N*-protecting groups in the reaction. *N*-methyl- and *N*-mesityl-(2,2-dimethyl-pent-4-enyl)-sulfonamides (**1f**, **1g**) were efficiently converted into the corresponding 1,3-aminoalcohols in good yields and complete regioselectivity (Table 2, entries 10 and 11) whereas substrate **1h** bearing an *o*-NO_2-benzenesulfonyl group failed to react (Table 2, entry 12). Interestingly, the *N*-Cbz protected substrate **1i** reacted smoothly to give the corresponding 1,3-aminoalcohol **2i** and 6,6-dimethyltetrahydropyrrolo[1,2-c]oxazol-3(1*H*)-one (**3i´´**) in a 2:1 ratio and 82% yield (Table 2, entry 13).[13] Internal substituted alkenes were efficiently transformed into the corresponding tertiary acetates as shown in entry 14.

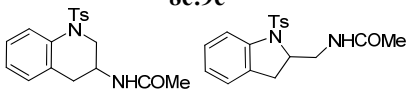
To our surprise, when scaling up the reaction of **1b**, traces of *N*-(5,5-diphenyl-1-tosylpiperidin-3-yl)acetamide (**8b**) were detected in the mixture. In this case, the acetonitrile used as solvent reacts as a nucleophile, followed by hydrolysis to the corresponding amide. Due to the broad range of biological activities reported for *N*-piperidin-3-yl carboxamides we decided to further pursue this synthetically useful transformation.[14] After an additional short screening of reaction conditions, aminoamidation products could be selectively obtained by reducing the amount of water in the reaction to only 2 equivalents. With these new optimized conditions we studied the scope of this transformation (Table 3).

Substrate **1a** afforded 1,3-aminoamide **8a** in 68% yield (Table 3, entry 1). 2,2-Diphenyl, 2,2-dimethyl and 2-cyclohexyl substituted substrates **1b-d** were efficiently transformed under these conditions into the corresponding cyclic 1,3-aminoamidation products **8b-d** in 72, 70 and 74% yield, respectively (Table 3, entries 2, 3 and 6). Aminoamide **8c** could be crystallized thus confirming the structure of these novel derivatives.[15] Propio- and butyronitrile could also be employed as shown in entries 4 and 5. The reactions proved to be highly regioselective except for aniline **1e** which afforded a 1:1 mixture of regioisomers **8e**

and **9e** in 70% combined yield (Table 3, entry 7). *N*-methyl- and *N*-mesityl-sulfonamides **1f** and **1g** afforded the corresponding products **8f** and **8g** in 64 and 46% yield respectively upon heating for 15 h (Table 3, entries 8 and 9).

Table 3. Scope of the gold-catalyzed aminoamidation reaction

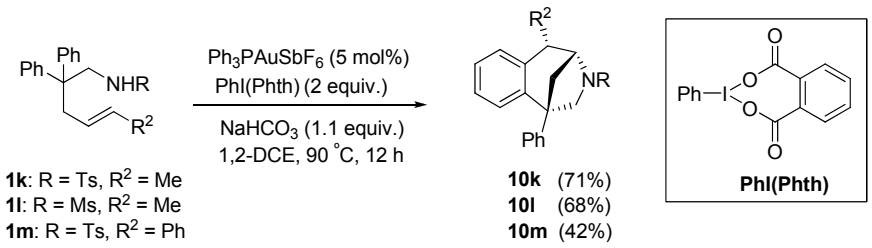


Entry	s.m.	Products: R, R^1, R^2 [a]	Yield, (%)[b]
1	**1a**	**8a**: R = Ts, R^1 = H, R^2 = Me [c]	68[d]
2	**1b**	**8b**: R = Ts, R^1 = Ph, R^2 = Me	72
3	**1c**	**8c**: R = Ts, R^1 = R^2 = Me	70
4	**„**	**8c´**: R = Ts, R^1 = Me, R^2 = Et	60
5	**„**	**8c´´**: R = Ts, R^1 = Me, R^2 = Pr	68
6	**1d**	**8d**: R = Ts, R^1 = -$(CH_2)_5$-, R^2 = Me	74
7	**1e**	**8e:9e**[e] 	70 [d]
8	**1f**	**8f**: R = Ms, R^1 = R^2 = Me	64[f]
9	**1g**	**8g**: R = Mesitylsulfonyl, R^1 = R^2 = Me,	46[f]
10	**1k**	**-**	-

[a] Determined by ^{1}H-NMR in the crude reaction mixture. [b] Isolated yield after column chromatography. [c] Regioisomeric mixture 9:1. [d] Isolated yield of the mixture. [e] Regioisomeric mixture 1:1. [f] Reaction time: 15 h

The 1,2-substitution pattern on the olefin seemed to be an intrinsic limitation for these gold-catalyzed aminooxygenation/amidation reactions (Table 2, entry 15 and Table 3, entry 10). However, the reaction of **1k** in the presence of a phthaloyl based iodosobenzene afforded tricyclic 3-benzazepine **10k**[16] in a diastereomerically pure form as a result of the activation of one of the aromatic rings at the C_2 position of the pentene backbone (Scheme 2).[17]

Scheme 2. Gold-catalyzed synthesis of tricyclic 3-benzazepines



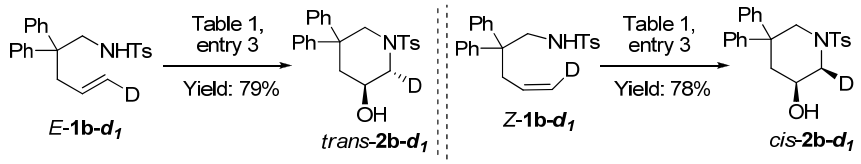
1k: R = Ts, R^2 = Me
1l: R = Ms, R^2 = Me
1m: R = Ts, R^2 = Ph

10k (71%)
10l (68%)
10m (42%)

The reaction was extended to related 1,2-disubstituted olefinic substrates **1l** and **1m**, which were converted into the tricycles **10l** and **10m** in good to moderate yields (Scheme 2). Compounds of type **10** largely incorporate the C-framework of aphanorphines, marine natural compounds that resemble benzomorphane analgesics such as pentazocine.[18]

To gain a deeper insight into the mechanism of these transformations, deuterium labelled alkenes *E*- and *Z*-**1b**-d_1 were prepared and subjected to the standard reaction conditions from Table 1 affording *trans*-**2b**-d_1 and *cis*-**2b**-d_1 respectively as single diastereoisomers (Scheme 3).[19]

Scheme 3. Deuterium labelling experiments

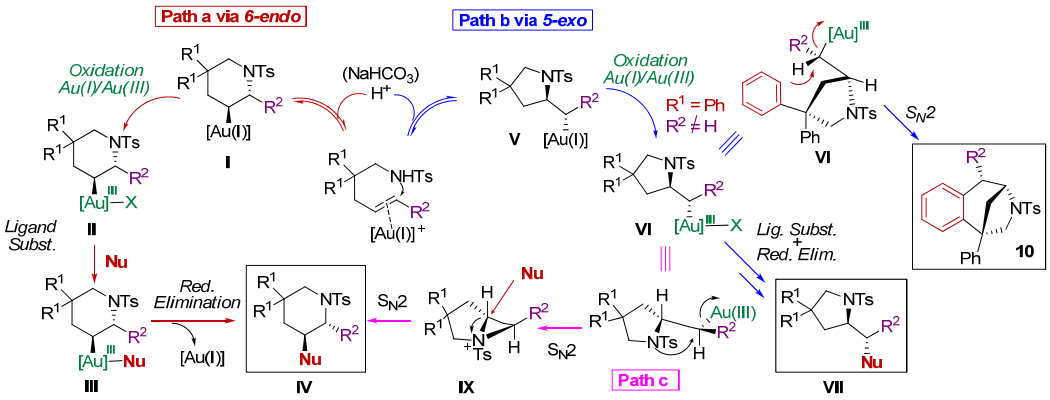


E-**1b**-d_1 | *trans*-**2b**-d_1 | *Z*-**1b**-d_1 | *cis*-**2b**-d_1

Based on these results, different mechanistic manifolds can be outlined as shown in Scheme 4. First, gold(I) can activate the alkene triggering the attack of the nitrogen in a *6-endo* fashion to form **I** upon deprotonation in the presence of base in a reversible step (path a, red). The lack of reactivity of Ph_3PAuCl compared to cationic $Ph_3PAuSbF_6$ supports the hypothesis of a gold(I) mediated *trans*-amino-auration of the alkene as first step in this process.[9d,20] In addition, the failure of **1h** to react seems to rule out the hypothesis of a gold(III)-amido intermediate in contrast to copper catalyzed processes.[6,21] Alkyl-gold(I) complex **I** can then undergo oxidation to give gold(III)-intermediate **II**. If Selectfluor is used, substitution of the fluorine ligand with a suitable nucleophile such as water or alcohol delivers intermediate **III**.[22] Due to the highly electrophilic nature of the gold(III) center, acetonitrile can also react as a nucleophile[23] being hydrolyzed in the presence of water to give intermediate **III** (Nu = NHCOMe).[24,25] Upon reductive elimination in **III** the new Csp^3-OH, Csp^3-OR and Csp^3-N bonds would be formed (**IV**). If $PhI(OAc)_2$ is used as oxidant direct reductive elimination in **II**, would afford the observed aminoacetoxylation products. This proposal allows to explain the relative configuration observed in the reactions shown in Scheme 3. Thus, no competing S_N2 type nucleophilic attack by the nucleophile on **II** would be operating in these reactions.[3,26]

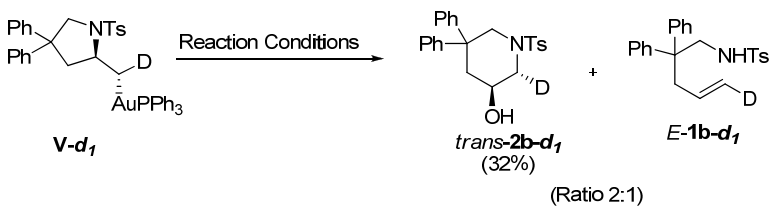
In contrast, a 5-*exo* cyclization mode via intermediate **V** (Scheme 4, path b, blue) following a similar oxidation sequence would yield complex **VI** accounting for the formation of the 5-membered ring products **VII**. In fact, for 1,2-disubstituted alkenes bearing an aromatic substituent in the backbone, the aryl can behave as a nucleophile in **VI** to produce tricyclic products **10** via nucleophilic substitution reaction.

Scheme 4. Mechanistic proposals



However, an alternative mechanism to explain the formation of **IV** from 5-*exo*-intermediate **VI** can also be outlined (Scheme 4, path c, pink). An aziridine intermediate **IX** can be obtained from **VI** via intramolecular nucleophilic attack of the *N*-moiety with concomitant metal departure.[27] Ring opening in the presence of an external nucleophile would afford compounds **IV**, in line with the relative configurations reported in Scheme 3. To test this hypothesis, intermediate **V-*d*$_1$**[20] was prepared and submitted to the reaction conditions affording *trans*-**2b-*d*$_1$** and *E*-**1b-*d*$_1$** in a 2:1 ratio (Scheme 5).[11,28] Although the transformation of **V** into **2b** is not a direct evidence of its participation in the reactions described herein, it seems to indicate that several reaction pathways can co-exist under the reaction conditions to explain the formation of the observed products.

Scheme 5. Mechanistic studies



In summary, the first gold-catalyzed aminooxygenation of unactivated alkenes and a novel alkene aminoamidation by gold activation of nitriles are reported here. The reactions are highly regioselective complementing 5-*exo*-Pd-catalyzed processes and expanding the scope

of Cu-mediated reactions. The work described herein opens up interesting mechanistic dichotomies of Au(I)/Au(III)-catalyzed transformations. In addition, tricyclic 3-benzazepines could be efficiently obtained in a diastereomerically pure form as a result of a gold-catalyzed oxidative arylation reaction. Further studies to apply the later process to the synthesis of complex natural products are currently underway in our laboratory.

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[5] See, for example: (a) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (b) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A.E.; Tang, P.; Goddard III, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132,* 3793.

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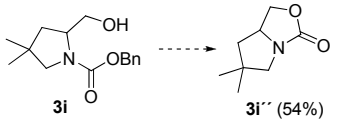
[11] For further experimental details, please see the Chapter IV: Experimental section, Supplementary data.

[12] The structure of both regioisomers **2** and **3** could be assigned based on the X-Ray diffraction of compound **2b** and by comparison with the analytical data reported for **3a** respectively: Miura, K.; Katsukiyo, T.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *Org. Lett.* **2000**, *2*, 385. The structure of the remaining products was assigned in analogy.

[13] Formation of **3ii´** can be explained from *5-exo* product (**3i**).



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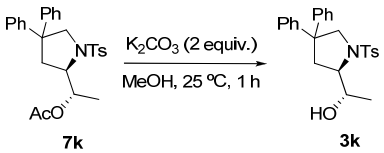
[15] See Chapter IV: Experimental Section, Crystallography data.

[16] In the presence of $PhI(OAc)_2$ as oxidant, pyrrolidine **7k** could be isolated in 5% yield. The relative configuration of **7j** was confirmed by X-Ray diffraction of alcohol **3k**, obtained by deprotection of the acetoxy group under basic conditions. In addition, the structure of **10k** was also confirmed by X-Ray diffraction (see Supplementary data).



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[19] Similar results were obtained in the aminoacetoxylation reaction, See Supplementary data.

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[23] For acetonitrile as nucleophile in gold processes: Barluenga, J.; Fernández-Rodríguez, M.A.; García-García, P.; Aguilar, E. *J. Am. Chem. Soc.* **2008**, *130*, 2764.

[24] For Au-catalyzed hydrolysis of nitriles: (a) Ramón, R. S.; Marion, N.; Nolan, S. P. *Chem. Eur. J.* **2009**, *15*, 8695; For Pt, see: (b) Jiang, X.; Minaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Org. Chem*. **2004**, *69*, 2327.

[25] A competition experiment was run with **1b** under conditions of Table 3 in the presence of 20 equiv. of ethyl amide. Only product **8b** was detected in the mixture suggesting that acetonitrile is the actual nucleophile being hydrolyzed to the amide under the reaction conditions.

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[27] Aziridine intermediates have been proposed to explain the formation of 6-*endo* products in a Pd-catalyzed alkoxyamination (ref. 2e). See also: Bowen, E. G.; Wardrop E. J. *Org. Lett.* **2010**, *12*, 5330.

[28] We would like to thank one of the referees for suggesting this insightful experiment.

Chapter 4

Experimental Section

Table of Contents

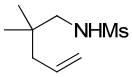
4.1 General information

NMR spectra were recorded on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual ^{1}H and ^{13}C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution electrospray ionization and electronic impact mass spectrometry was performed on a Finnigan MAT 900 (Thermo Finnigan, San Jose, CA; USA) doublefocusing magnetic sector mass spectrometer. Ten spectra were acquired. A mass accuracy ≤ 2 ppm was obtained in the peak matching acquisition mode by using a solution containing 2 <l PEG200, 2 <l PPG450, and 1.5 mg NaOAc (all obtained from Sigma-Aldrich, CH-Buchs) dissolved in 100ml MeOH (HPLC Supra grade, Scharlau, E-Barcelona) as internal standard. GC-MS analysis was done on a Finnigan Voyager GC8000 Top.

Materials and Methods: Unless otherwise stated, starting materials were purchased from Aldrich and/or Fluka. All reagents were used as received. Starting materials were prepared according to previously reported procedures.[1] Substrates **1a**[1b]**, 1b**[2], **1c**,[1b] **1d**,[2] **1e**,[1b] **1g**,[3] **1h**[4] and where already reported in the literature. PhI(Phth) was synthesized in analogy to a previously reported procedure.[5] $Ph_3PAuSbF_6$ was prepared from Ph_3PAuCl (1 equiv.) and $AgSbF_6$ (1 equiv.) in DCE (0.05 M). Except acetonitrile, solvents were purchased in HPLC quality, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Unless otherwise stated, reactions were not run under inert atmosphere. Conversion was monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. Flash column chromatography was performed over silica gel (230-400 mesh).

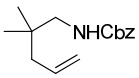
4.2 Characterization of starting materials

***N*-Mesyl-2,2-dimethyl-4-pentenyl amine (1f)**



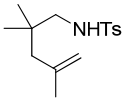
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81-5.72 (m, 1H), 5.06-5.01 (m, 2H), 4.68 (t, *J* = 6.9 Hz, 1H), 2.91 (s, 3H), 2.86 (d, *J* = 6.7 Hz, 2H), 1.99 (dt, *J* = 7.5, 1.1 Hz, 2H), 0.90 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.2, 118.0, 52.9, 44.0, 39.9, 34.2, 24.8. IR (film): $\tilde{\upsilon}$ = 3291, 2964, 1435, 1318, 1275, 1265, 1153, 1068, 749 cm^{-1}. HRMS (ESI): *m/z*: calcd for $C_8H_{17}NO_2SNa$: 214.0872. Found: 214.0873.

***N*-Carbobenzyloxy-2,2-dimethyl-4-pentenyl amine (1i)**



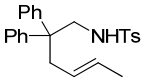
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.31 (m, 5H), 5.88-5.76 (m, 1H), 5.10 (s, 2H), 5.06-5.01 (m, 2H), 4.78 (bs, 1H), 3.02 (d, J = 6.4 Hz, 2H), 1.97 (d, J = 6.4 Hz, 2H), 0.88 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 137.1, 135.2, 120.0, 128.7, 128.6, 118.1, 67.2, 51.3, 44.8, 35.2, 25.2. IR (film): $\tilde{\upsilon}$ = 3443, 3339, 1704, 1538, 1518, 1242, 909, 731 cm^{-1}.

***N*-Tosyl-4-methyl-2,2-dimethyl-4-pentenyl amine (1j)**



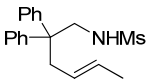
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 4.84 (m, 1H), 4.61 (m, 1H), 4.47 (7, J = 6.9 Hz, 1H), 2.71 (d, J = 7.1 Hz, 2H), 2.42 (s, 3H), 1.94 (s, 2H), 1.73 (s, 3H), 0.89 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 143.2, 137.5, 130.2, 127.6, 115.4, 54.0, 47.9, 35.2, 26.0, 25.6, 22.0. IR (film): $\tilde{\upsilon}$ = 3282, 2965, 1324, 1160, 1094, 907, 730 cm^{-1}. HRMS (ESI): *m/z*: calcd for $C_{15}H_{23}NO_2SNa$: 304.1341. Found: 304.134.

***N*-Tosyl-5-methyl-2,2-diphenyl-4-pentenyl amine (1k)**



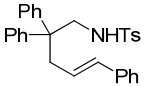
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.2 Hz, 2H), 7.29-7.21 (m, 8H), 7.06-7.04 (m, 4H), 5.31-5.32 (m, 1H), 4.90-4.82 (m, 1H), 3.83 (t, J = 6.1 Hz, 1H), 3.52 (d, J = 6.7 Hz, 2H), 2.81 (d, J = 6.7 Hz, 2H), 2.44 (s, 3H), 1.49 (dd, J = 6.4, 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.3, 143.9, 136.7, 130.2, 130.2, 128.9, 128.3, 127.7, 127.1, 125.7, 50.1, 49.6, 40.5, 22.0, 18.4. IR (film): $\tilde{\upsilon}$ = 3291, 3028, 2918, 1598, 1496, 1408, 1162, 1093, 973, 907, 729, 700. HRMS (ESI): *m/z*: calcd for $C_{25}H_{27}NO_2SNa$: 428.1654. Found: 428.1661.

***N*-Mesyl-5-methyl-2,2-diphenyl-4-pentenyl amine (1l)**



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.15 (m, 10H), 5.52-5.57 (m, 1H), 5.01-4.95 (m, 1H), 3.80-3.75 (m, 3H), 2.89 (d, J = 6.9 Hz, 2H), 2.64 (s, 3H), 1.56 (dd, J = 6.4, 1.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 129.7, 128.4, 127.9, 126.7, 125.5, 48.8, 49.7, 40.1, 39.8, 18.0. IR (film): $\tilde{\upsilon}$ = 3294, 3025, 2933, 1495, 1444, 1406, 1318, 1151, 1078, 970, 907, 730, 699. HRMS (ESI): *m/z*: calcd for $C_{19}H_{23}NO_2SNa$: 352.1341 Found: 352.1343.

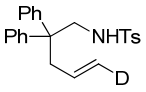
***N*-Tosyl-5-phenyl-2,2-diphenyl-4-pentenyl amine (1m)**



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.4 Hz, 2H), 7.29-7.06 (m, 17H), 6.25 (d, J = 16.1 Hz, 1H), 5.59 (dt, J = 16.1, 7.4 Hz, 1H), 3.84 (t, J = 6.5 Hz, 1H), 3.55 (d, J = 6.4 Hz, 2H), 3.02 (dd, J = 7.3, 1.0 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =

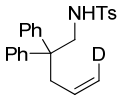
144.6, 143.4, 137.4, 136.2, 134.1, 129.7, 128.5, 128.3, 127.7, 127.2, 127.1, 126.8, 126.2, 124.8, 50.0, 49.2, 40.1, 21.5. IR (film): $\tilde{\upsilon}$ = 3294, 3025, 2933, 1329, 1162, 912, 745, 699. HRMS (ESI): *m/z*: calcd for $C_{30}H_{29}NO_2SNa$: 490.1811. Found: 490.1814.

(*E*)-*N*-Tosyl-5-deutero-2,2-diphenyl-4-pentenyl amine (*E*-1b-d_1)



Compound ***E*-1b-d_1** was synthesized in analogy to a previously reported procedure.[6] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.5 Hz, 2H), 7.28-7.20 (m, 8H), 7.07-7.04 (m, 4H), 6.28 (dt, *J* = 16.7, 7.1 Hz, 1H), 4.93 (dt, *J* = 16.7, 1.3 Hz, 1H), 3.86 (t, *J* = 6.6 Hz, 1H), 3.52 (d, *J* = 6.4 Hz, 2H), 2.90 (dd, *J* = 7.1, 1.1 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 143.9, 136.8, 133.5, 130.2, 128.9, 128.3, 127.7, 127.2, 119.5-119.1 (m, CD), 49.9, 49.8, 41.7, 22.0. IR (film): $\tilde{\upsilon}$ = 3291, 3026, 3030, 2926, 2858, 1597, 1494, 1445, 1408, 1327, 1160, 1092, 1077, 776, 663. HRMS (ESI): *m/z*: calcd for $C_{24}H_{24}DNO_2SNa$: 415.1561. Found: 415.1564.

(*Z*)-*N*-Tosyl-5-deutero-2,2-diphenyl-4-pentenyl amine (*Z*-1b-d_1)

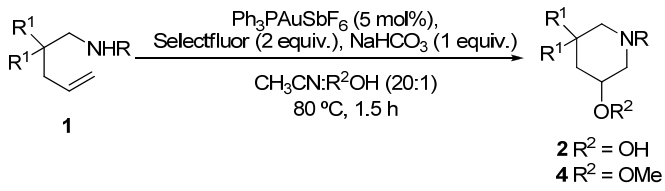


Compound ***Z*-1b-d_1** was synthesized in analogy to a previously reported procedure[1] from (*Z*)-3-deuterioallyl bromide[7]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.1 Hz, 2H), 7.29-7.21 (m, 8H), 7.07-7.05 (m, 4H), 5.31-5.24 (m, 1H), 4.92 (d, *J* = 10.1 Hz, 1H), 3.83 (t, *J* = 6.5 Hz, 1H), 3.52 (d, *J* = 6.4 Hz, 2H), 2.90 (dd, *J* = 7.1, 0.8 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 143.4, 136.2, 133.0, 129.7, 128.4, 127.8, 127.2, 126.7, 119-118 (m, CD), 49.4, 49.3, 41.2, 21.5 IR (film): $\tilde{\upsilon}$ = 3284, 3055, 3030, 2926, 1598, 1495, 1329, 1162, 1093, 755, 699. HRMS (ESI): *m/z*: calcd for $C_{24}H_{24}DNO_2SNa$: 415.1561. Found: 415.1559.

4.3 General procedure for gold catalyzed aminooxygenation, aminoamidation and aminoarylation

4.3.1 General procedures for gold catalyzed aminooxygenation

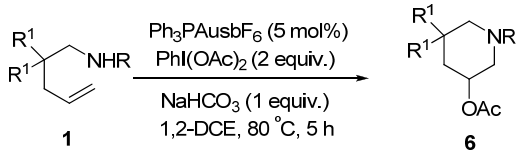
Conditions A, B and B' (Table 2)



A mixture of aminopent-4-ene (**1**, 1 equiv.), Selectfluor (2 equiv.) and $NaHCO_3$ (1 equiv.) was dissolved in MeCN:H_2O (20:1, 0.02 M) or alternatively in MeCN: (MeOH or EtOH)

(20:1, 0.02 M) followed by addition of $Ph_3PAuSbF_6$ (0.05 equiv.). The reaction was stirred for 1.5 h at 80 °C and was monitored by TLC. Upon consumption of the starting material, the mixture was diluted with DCM (5 ml) and water (2 ml) was added. The mixture was extracted with DCM (3 x 5 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified through silica gel flash column chromatography (Hexane/EtOAc = 6/1) to yield the desired aminoalcohols **2** or aminoethers **4**.

Conditions C (Table 2) and also Scheme 2

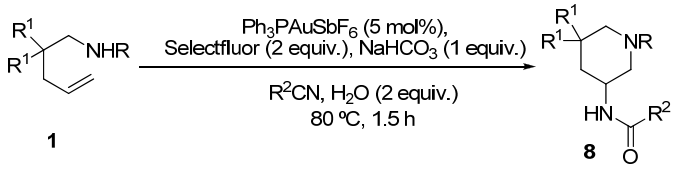


1 6

A mixture of aminopent-4-ene (**1**, 1 equiv.), $PhI(OAc)_2$ (2 equiv.) and $NaHCO_3$ (1 equiv.) was dissolved in 1,2-dichloroethane (0.1 M) followed by addition of $Ph_3PAuSbF_6$ (0.05 equiv.). The reaction was stirred for 5 h at 80 °C and was monitored by TLC. Upon consumption of the starting material, the mixture was diluted with DCM (5 ml) and filtered over Celite. The solvent was evaporated under reduced pressure and the residue was purified through silica gel flash column chromatography (Hexane/EtOAc = 10/1) to yield the desired aminoacetates **6**.

4.3.2 General procedures for gold catalyzed aminoamidation

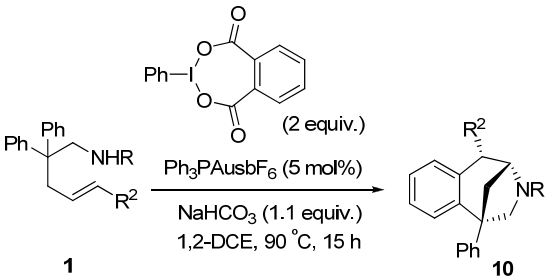
Conditions Table 3



1 8

A mixture of aminopent-4-ene (**1**, 1 equiv.), Selectfluor (2 equiv.) and $NaHCO_3$ (1 equiv.) was dissolved in acetonitrile or propionitrile or butyronitrile (0.02 M) and H_2O (2 equiv.), followed by addition of $Ph_3PAuSbF_6$ (0.05 equiv.). The reaction was stirred for 1.5 h at 80 °C and was monitored by TLC. Upon consumption of the starting material, the mixture was diluted with DCM (5 ml) and filtered over Celite washing with DCM (2.5 ml) and EtOAc (2.5 mL). The solvent was evaporated under reduced pressure and the residue was purified through silica gel flash column chromatography (Hexane/EtOAc = 1/1 to 0/100) to yield the desired aminoamides **8**.

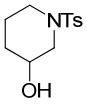
4.3.3 General procedures for gold catalyzed aminocarbonylation.



A mixture of the corresponding aminopent-4-ene (**1**, 1 equiv.), PhI(Phth) (2 equiv.) and $NaHCO_3$ (1 equiv.) was dissolved in 1,2-dichloroethane (0.1 M) followed by addition of $Ph_3PAuSbF_6$ (0.05 equiv.). The reaction was stirred for 15 h at 90 ^oC and was monitored by TLC. Upon consumption of the starting material, the mixture was diluted with DCM (5 ml) and filtered over Celite. The solvent was evaporated under reduced pressure and the residue was purified through silica gel flash column chromatography (Hexane/EtOAc = 20/1) to yield the desired products **10**.

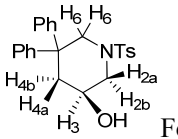
4.4 Characterization of products

1-Tosylpiperidin-3-ol (2a)[8]



Following the general procedure of aminooxygenation (conditions A) compound **2a** was isolated in 78% yield as a regioisomeric mixture (9:1[9]); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 3.86-3.85 (m, 1H), 3.31 (dd, J = 11.1, 3.5 Hz, 1H), 3.13-3.09 (m, 1H), 2.78 (td, J = 8.4, 3.5 Hz, 1H), 2.70 (dd, J = 11.1,7.1 Hz, 1H), 2.43 (s, 3H), 2.03 (bs, 1H), 1.87-1.43 (m, 3H), 143-1.34 (m,1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1, 133.7, 130.2, 128.2, 66.2, 53.0, 46.7, 32.2, 22.3, 22.0.

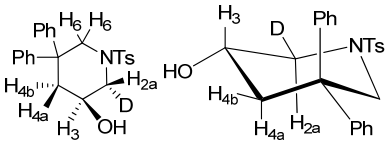
5,5-Diphenyl-1-tosylpiperidin-3-ol (2b)[4]



Following the general procedure of aminooxygenation (conditions A) compound **2b** was isolated in 85% yield as a regioisomeric mixture (9:1); ^1H NMR (400 MHz, $CDCl_3$): 7.67 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.37-7.21 (m, 10H), 4.31 (d, J = 12.7 Hz, $1H_6$), 3.83-3.80 (m, $1H_3$), 3.76 (m, 1 H_{2b}), 2.77 (dd, J =12.3, 1.3 Hz, 1 H_{4b}), 2.64 (d, J = 12.7, $1H_6$), 2.45 (s, 3H), 2.33 (dd, J = 9.4, 9.4 Hz, $1H_{2a}$), 2.12 (dd, J = 12.3, 10.1 Hz, $1H_{4a}$), 1.79 (brs, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 144.2, 143.9, 132.2, 129.8, 128.6, 128.5, 127.8, 127.7, 126.8, 126.7, 126.3, 64.6, 53.9, 52.6, 46.2, 43.2, 21.5. IR

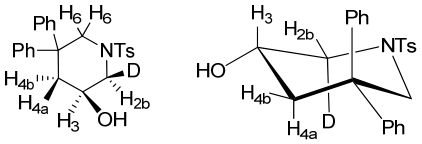
(film): $\tilde{\upsilon}$ = 3512, 1738, 1597m 1495, 1340, 1162, 1034, 907, 804, 785, 728, 698, 661, 564 cm^{-1}; MS (EI): *m/z*: calcd for $C_{24}H_{25}NNaO_3S$: 430.1, found: 430.2.

***Trans*-2b-*d*$_1$**



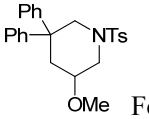
Following the general procedure of aminooxygenation (conditions A) compound ***Trans*-2b-d1** was isolated in 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.37-7.21 (m, 10H), 4.31 (d, *J* = 12.7 Hz, $1H_6$), 3.83-3.80 (m, $1H_3$), 2.77 (dd, *J* =12.3, 1.3 Hz, $1H_{4b}$), 2.64 (d, *J* = 12.7, $1H_{6b}$), 2.45 (s, 3H), 2.33 (d, J = 9.4 Hz, $1H_{2a}$), 2.12 (dd, *J* = 12.3, 10.1 Hz, $1H_{4a}$), 1.79 (brs, 1H, OH). HRMS (EI): *m/z*: calcd for $C_{24}H_{24}DNNaO_3S$: 431.1516, found: 431.1510.

***Cis*-2b-*d*$_1$**



Following the general procedure of aminooxygenation (conditions A) compound ***Cis*-2b-d1** was isolated in 78% yield ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.37-7.21 (m, 10H), 4.31 (d, *J* = 12.7 Hz, $1H_6$), 3.83-3.80 (m, $1H_3$), 3.76 (d, *J* = 2.1 Hz, $1H_{2b}$), 2.77 (dd, *J* =12.3 1.3 Hz, $1H_{4b}$), 2.64 (d, *J* = 12.7 Hz, $1H_{6b}$), 2.45 (s, 3H), 2.12 (dd, *J* = 12.3, 10.1 Hz, $1H_{4a}$), 1.79 (brs, 1H, OH). HRMS (EI): *m/z*: calcd for $C_{24}H_{24}DNNaO_3S$: 431.1516, found: 431.1510.

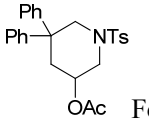
3-Methoxy-5,5-diphenyl-1-tosylpiperidine (4b)



Following the general procedure of aminooxygenation (conditions B) compound **4b** was isolated in 87% yield as a regioisomeric mixture (9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.5 Hz, 2H), 7.47 (dd, *J* = 8.5, 1.1 Hz, 2H), 7.33-7.09 (m, 10H), 4.56 (d, *J* = 12.7 Hz, 1H), 4.04 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.28 (s, 3H), 3.25-3.19 (m, 1H), 2.83 (dquint, *J* = 12.7, 1.7 Hz, 1H), 2.38 (s, 3H), 2.22 (d, *J* = 12.1 Hz, 1H), 1.94 (t, *J* = 10.1 Hz, 1H), 1.84 (dd, *J* = 12.5, 11.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.2, 143.9, 143.8, 132.3, 129.8, 128.6, 128.5, 127.9, 127.7, 126.7, 126.5, 126.2, 73.0, 56.7, 54.2, 49.9, 46.3, 41.1, 21.5.

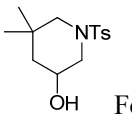
IR (film): $\tilde{\upsilon}$ = 2929, 1597, 1495, 1447, 1344, 1163, 1089, 908, 783, 730, 700, 661. HRMS (ESI): *m/z*: calcd for $C_{25}H_{27}NO_3SNa$: 444.1603. Found: 444.1600.

3-Acetoxy-5,5-diphenyl-1-tosylpiperidine (6b)



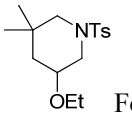
Following the general procedure of aminooxygenation (conditions C) compound **6b** was isolated in 79% yield as a regioisomeric mixture (4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.5 Hz, 2H), 7.40 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.32-7.10 (m, 10H), 4.78 (sept, *J* = 4.8 Hz, 1H), 4.20 (d, *J* = 10.9 Hz, 1H), 3.67 (dd, *J* = 10.6, 4.2 Hz, 1H), 2.80 (d, *J* = 12.1 Hz, 2H), 2.46 (t, *J* = 9.5 Hz, 1H), 2.38 (s, 3H), 2.13 (dd, *J* = 12.5, 10.1 Hz, 1H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 145.7, 143.9, 143.4, 132.5, 129.8, 128.7, 128.5, 127.8, 127.6, 126.5, 126.5, 66.9, 54.0, 49.2, 46.0, 39.5, 21.6, 20.9. (One carbon signal is missing due to overlapping). IR (film): $\tilde{\upsilon}$ = 3060, 3030, 2963, 1736, 1597, 1495, 1346, 1163, 1042, 907, 727, 699. HRMS (ESI): *m/z*: calcd for $C_{26}H_{28}NO_4S$: 450.1733. Found: 450.1738.

5,5-Dimethyl-1-tosylpiperidin-3-ol (2c)[4]



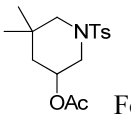
Following the general procedure of aminooxygenation (conditions A) compound **2c** was isolated in 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 3.97 (sept, *J* = 4.8 Hz, 1H), 3.81 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.19 (dd, *J* = 11.1, 1.3 Hz, 1H), 2.42 (s, 3H), 2.03 (bs, 1H), 2.00 (dd, *J* = 9.6, 8.2 Hz, 2H), 1.70 (dd, *J* = 12.7, 4.4 Hz, 1H), 1.05 (s, 3H), 0.99 (dd, *J* = 12.7, 10.7 Hz, 1H), 0.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 133.4, 129.7, 127.5, 64.6, 56.7, 52.6, 46.0, 31.9, 28.6, 25.0, 21.5.

3-Acetoxy-5,5-dimethyl-1-tosylpiperidine (4c')



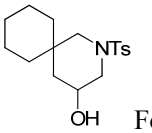
Following the general procedure of aminooxygenation (conditions B') compound **4c'** was isolated in 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 4.99 (ddt, *J* = 10.7, 4.8, 1.7 Hz, 1H), 3.63-3.48 (m, 3H), 3.25 (dt, *J* = 10.7, 1.7 Hz, 1H), 2.41 (s, 3H), 1.95-1.97 (m, 2H), 2.32 (ddt, *J* = 12.7, 4.6, 1.7 Hz, 1H), 1.15 (t, *J* = 6.7 Hz, 3H), 1.06 (s, 3H), 0.96-0.9 (m, 1H), 0.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 133.9, 130.1, 128.0, 72.1, 64.8, 57.5, 50.7, 44.3, 32.3, 29.2, 25.4, 22.0, 16.0. IR (film): $\tilde{\upsilon}$ = 2972, 2928, 1343, 1162, 1094, 989, 966, 774. HRMS (ESI): *m/z*: calcd for $C_{16}H_{26}NO_3S$: 3291893. Found: 329.1896.

3-Acetoxy-5,5-dimethy-1-tosylpiperidine (6c)



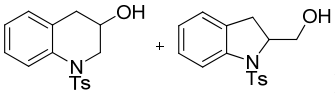
Following the general procedure of aminooxygenation (conditions C) compound **6c** was isolated in 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 4.99 (sept, J = 4.6 Hz, 1H), 3.59 (dd, J = 10.1, 4.6 Hz, 1H), 3.02 (d, J = 11.3 Hz, 1H), 2.43 (s, 3H), 2.32 (d, J = 11.3 Hz, 1H), 2.01(s, 3H), 1.68 (dd, J = 12.5, 4.6 Hz, 1H), 0.99 (dd, J = 12.5, 10.1 Hz, 2H), 1.06 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 143.5, 133.6, 129.7, 127.5, 66.9, 56.8, 49.2, 41.9, 31.7, 28.0, 25.6, 21.5, 21.1. IR (film): $\tilde{\upsilon}$ = 2957, 1735, 1467, 1345, 1238, 1161, 1092, 1038, 996, 773. HRMS (ESI): *m/z*: calcd for $C_{16}H_{23}NO_4SNa$: 348.1243. Found: 348.1244.

5,5-Ciclohexyl-1-tosylpiperidin-3-ol (2d)[4]



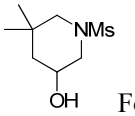
Following the general procedure of aminooxygenation (conditions A) compound **2d** was isolated in 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 4.01-3.96 (m, 1H), 3.81 (dd, J = 10.7, 4.8 Hz, 1H), 3.52 (d, J = 10.7 Hz, 1H), 2.42 (s, 3H), 2.04 (t J = 9.7, 1H), 1.98 (d, J = 11.6 Hz, 1H), 1.90-1.85 (m, 2H), 1.62-1.24 (m, 10H), 0.99 (dd, J = 12.7, 12.9, 10.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 134.1, 130.2, 127.9, 64.5, 54.6, 53.6, 44.8, 37.9, 35.1, 33.3, 26.8, 22.0, 21.8. (One C is overlapping).

1-Tosyl-1,2,3,4-tetrahydroquinolin-3-ol (2e) and (1-tosylindolin-2-yl)methanol (3e)



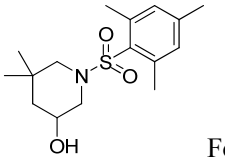
Following the general procedure of aminooxygenation (conditions A) compound **2e** and **3e** was isolated in 50% yield as a regioisomeric mixture (1.5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.22-7.03 (m, 10H), 4.31-3.27 (m, 1H), 4.04-4.01 (m, 2H), 3.72 (t, J = 5.9 Hz, 2H), 3.63-3.58 (m, 1H), 2.83-2.75 (m, 2H), 2.65-2.37 (m, 3H), 2.38 (s, 3H), 2.35 (s, 3H), 1.93 (d, J = 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 144.4, 141.9, 137.4, 136.8, 135.0, 132.6, 130.4, 130.3, 130.3, 130.2, 128.4, 128.2, 127.8, 127.7, 127.6, 127.5, 125.7, 125.6, 124.2, 118.2, 66.2, 64.8, 64.1, 52.7, 36.5, 31.8, 22.1. IR (film): $\tilde{\upsilon}$ = 3508, 2923, 1597, 1488, 1343, 1159, 1089, 961, 757, 664. HRMS (ESI): *m/z*: calcd for $C_{16}H_{17}NO_3SNa$: 326.0821. Found: 326.0823.

5,5-Dimethyl-1-(methylsulfonyl)piperidin-3-ol (2f)



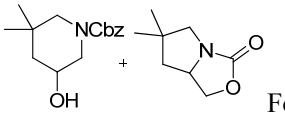
Following the general procedure of aminooxygenation (conditions A) compound **2f** was isolated in 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (sept, J = 4.6 Hz, 1H), 3.80 (dd, J = 11.2, 4.6 Hz, 1H), 3.21 (d, J = 11.2 Hz, 1H), 2.75 (s, 3H), 2.43-2.35 (m, 2H), 1.96 (bs, 1H), 1.78 (dd, J = 12.7, 4.6 Hz, 1H), 1.14 (dd, J = 12.7, 10.1 Hz, 1H), 1.02 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.2, 57.1, 52.7, 46.6, 35.7, 32.6, 29.0, 25.4. HRMS (ESI): *m/z*: calcd for $C_8H_{17}NO_3SNa$: 230.0821. Found: 230.0822.

5,5-Dimethyl-1-mesitylsulfonylpiperidin-3-ol (2g)



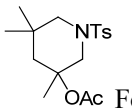
Following the general procedure of aminooxygenation (conditions A) compound **2g** was isolated in 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 2H), 3.92-3.88 (m, 1H), 3.61 (dd, J = 11.2, 4.4 Hz, 1H), 3.07 (dt, J = 11.2, 1.7 Hz, 1H), 2.61 (s, 6H), 2.58-2.52 (m, 1H), 2.45 (dd, J = 11.2, 10.2 Hz, 1H), 2.29 (s, 3H), 1.75 (dd, J = 12.7, 4.6 Hz, 1H), 1.63 (bs, 1H), 1.18 (dd, J = 12.7, 10.2 Hz, 1H), 0.96 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 140.3, 131.9, 131.8, 64.6, 55.4, 50.8, 46.4, 32.0, 28.7, 25.2, 22.9, 20.9. IR (film): $\tilde{\upsilon}$ = 3441, 2935, 2852, 1603, 1565, 1308, 1152, 1079, 985, 776, 660. HRMS (ESI): *m/z*: calcd for $C_{16}H_{25}NO_3SNa$: 334.1447. Found: 334.1448.

5,5-Dimethyl-1-carbobenzyloxypiperidin-3-ol (2i) and 6,6-dimethyltetrahydropyrrolo[1,2-c]oxazol-3(1*H*)-one (3i´´)



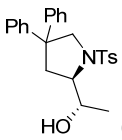
Following the general procedure of aminooxygenation (conditions A) compounds **2i** and **3i''** were isolated as a mixture (1:1) in 82% yiled; ^{1}H NMR (400 MHz, $CDCl_3$): Characterization of **2i**: δ = 7.36-7.35 (m, 5H), 5.13 (d, J = 2.6 Hz, 2H), 4.28-4.20 (m, 1H), 3.87-3.81 (m, 1H), 3.73-3.58 (m,1H), 2.65-2.57 (m, 2H), 1.79-1.75 (m, 1H), 1.59 (bs, 1H), 1.22 (dd, J = 12.7, 10.5 Hz, 1H), 0.97 (s, 3H), 0.90 (s, 3H). Characterization of **3i''**: δ = 4.50 (s, 1H), 4.12-4.08 (m, 2H), 3.38 (d, J = 11.3 Hz, 1H), 2.92 (d, J = 11.3 Hz, 1H), 1.83 (dd, J = 12.2, 6.0 Hz, 1H), 1.44 (dd, J = 12.2, 9.5 Hz, 1H), 1.15 (s, 3H), 1.14 (s, 3H). MS (ESI) (mixture): *m/z*: calcd for $C_{15}H_{21}NO_3SNa$: 286.2. Found: 286.2. *m/z*: calcd for $C_8H_{13}NO_2Na$: 178.1. Found: 178.1.

3-Acetoxy-5,5-dimethyl-3-methyl-1-tosylpiperidine (2j)



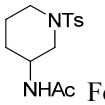
Following the general procedure of aminooxygenation (conditions C) compound **2j** was isolated in 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 4.00 (d, *J* = 11.3 Hz, 1H), 3.32 (d, *J* = 11.3 Hz, 1H), 2.42 (s, 3H), 2.24-2.13 (m, 3H), 1.98 (s, 3H), 1.44 (s, 3H), 1.11-1.08 (m, 1H), 1.06 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 143.3, 134.5, 129.7, 127.4, 78.2, 57.1, 54.2, 45.7, 31.2, 29.2, 25.3, 24.1, 22.5, 21.5. IR (film): $\tilde{\upsilon}$ = 2959, 1735, 1344, 1253, 1216, 1161, 911, 768. HRMS (ESI): *m/z*: calcd for $C_{17}H_{25}NO_4SNa$: 362.1396. Found: 362.1399.

(±)(*S*)-1-((*R*)-4,4-diphenyl-1-tosylpyrrolidin-2-yl)ethanol (3k)



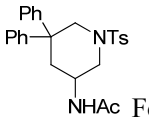
Compound **3k** was obtained obtained by deprotection of the acetoxy group of (S)-1-((R)-4,4-diphenyl-1-tosylpyrrolidin-2-yl)ethyl acetate (**7k**) under basic conditions; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.4 Hz, 2H), 7.24-7.04 (m, 12H), 4.44 (dd, *J* = 10.9, 1.8 Hz, 1H), 4.34 (qd, *J* = 6.4, 1.8 Hz, 1H), 4.07 (d, *J* = 10.9 Hz, 1H), 3.70 (ddd, *J* = 10.1, 6.4, 2.1 Hz, 1H), 2.80 (ddd, *J* = 12.7, 6.4, 1.6 Hz, 1H), 2.54 (dd, *J* = 12.7, 10.1 Hz, 2H), 2.36 (s, 3H), 1.19 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 144.0, 143.1, 135.2, 129.6, 128.6, 128.5, 126.9, 126.6, 126.5, 126.5, 126.1, 67.2, 65.2, 60.5, 52.2, 37.4, 21.4, 17.9. IR (film): $\tilde{\upsilon}$ = 3518, 3037, 1597, 1335, 1157, 1091, 1031, 1011, 754, 700, 666. HRMS (ESI): *m/z*: calcd for $C_{25}H_{27}NO_3SNa$: 444.1603. Found: 444.1604

***N*-(1-Tosylpiperidin-3-yl)acetamide (8a)**



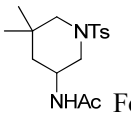
Following the general procedure of aminoamidation in acetonitrile, compound **8a** was isolated in 68% yield as a regioisomeric mixture (9:1); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.60 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 5.81 (bs, 1H), 4.06-3.99 (m, 1H), 3.17-3.11 (m, 1H), 2.93 (d, *J* = 4.4 Hz, 1H), 2.76 (ddd, *J* = 116, 8.8, 3.4 Hz, 1H), 2.43 (s, 3H), 1.93 (s, 3H), 1.81-1.49 (m, 5H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.1, 143.9, 132.9, 129.7, 127.6, 50.6, 46.5, 44.3, 28.4, 23.1, 21.7, 21.2. IR (film): $\tilde{\upsilon}$ = 3379, 3292, 2933, 2863, 1655, 1544, 1340, 1166, 1091, 748. HRMS (ESI): *m/z*: calcd for $C_{14}H_{20}N_2O_3SNa$: 319.1086. Found: 319.1086.

***N*-(5,5-Diphenyl-1-tosylpiperidin-3-yl)acetamide (8b)**



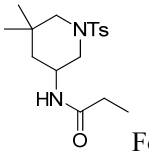
Following the general procedure of aminoamidation in acetonitrile, compound **8b** was isolated in 72% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.62 (d, *J* = 8.3 Hz, 2H), 7.39-7.18 (m, 12H), 5.21 (d, *J* = 8.3 Hz, 1H), 4.15-4.05 (m, 1H), 3.66-3.63 (m, 1H), 3.39-3.33 (m, 1H), 3.13-3.10 (m, 1H), 2.90-2.87 (m, 1H), 2.49-2.38 (m, 2H), 2.40 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.0, 145.8, 145.2, 144.2, 132.2, 129.8, 128.7, 128.6, 127.7, 127.0, 126.6, 126.5, 54.2, 50.5, 45.2, 43.6, 38.7, 22.7, 21.2. (One carbon signal is missing due to overlapping). IR (film): $\tilde{\upsilon}$ = 3305, 3061, 2967, 1655, 1597, 1540, 1344, 1162, 1090, 989, 700, 667. HRMS (ESI): *m/z*: calcd for $C_{26}H_{28}N_2O_3SNa$: 471.1712. Found: 471.1716.

***N*-(5,5-Dimethyl-1-tosylpiperidin-3-yl)acetamide (8c)**



Following the general procedure of aminoamidation in acetonitrile, compound **8c** was isolated in 70% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.60 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.38 (d, *J* = 6.6 Hz, 1H), 4.11-4.02 (m, 1H), 3.77 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.16 (d, *J* = 11.5, 1H), 2.42 (s, 3H), 2.07 (d, *J* = 11.5 Hz, 1H), 1.94 (d, *J* = 10.7 Hz, 1H), 1.90 (s, 3H), 1.56 (dd, *J* = 12.7, 4.4 Hz, 1H), 1.06 (s, 3H), 0.99 (dd, *J* = 12.5, 11.5 Hz, 1H), 0.94 (s, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.4, 143.7, 133.5, 129.6, 127.4, 56.8, 50.4, 43.6, 42.9, 31.4, 28.1, 24.6, 23.0, 21.2. IR (film): $\tilde{\upsilon}$ = 3282, 2952, 2849, 1654, 1540, 1340, 1308, 1091, 1034, 969, 812, 708, 665. HRMS (ESI): *m/z*: calcd for $C_{16}H_{24}N_2O_3SNa$: 347.1399. Found: 347.1400.

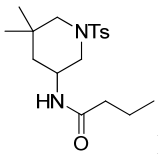
***N*-(5,5-Dimethyl-1-tosylpiperidin-3-yl)propionamide (8c')**



Following the general procedure of aminoamidation in propionitrile, compound **8c'** was isolated in 60% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.60 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.38 (d, *J* = 7.6 Hz, 1H), 4.12-4.03 (m, 1H), 3.74 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.15 (d, *J* = 11.5, 1H), 2.15-2.06 (m, 3H), 2.42 (s, 3H), 1.93 (t, *J* = 10.4 Hz, 1H), 1.58 (dd, *J* = 12.7, 4.5 Hz, 1H), 1.08 (t, *J* = 7.8 Hz, 3H), 1.06 (s, 3H), 0.99 (dd, *J* = 12.7, 11.5 Hz, 1H), 0.94 (s, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 172.9, 143.7, 133.6, 129.7, 127.4, 56.8, 50.4, 43.4, 42.9, 31.4, 29.5, 28.2, 24.6, 21.2, 9.5. IR (film): $\tilde{\upsilon}$ = 3296, 2958, 2872,

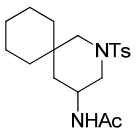
1646, 1536, 1340, 1159, 1091, 990, 812, 660. HRMS (ESI): *m/z*: calcd for $C_{17}H_{26}N_2O_3SNa$: 361.1556. Found: 361.1556.

***N*-(5,5-Dimethyl-1-tosylpiperidin-3-yl)butyramide (8c'')**



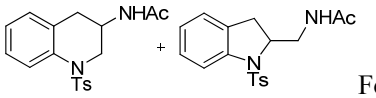
Following the general procedure of aminoamidation in butyronitrile, compound **8c''** was isolated in 68% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.60 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.26 (d, *J* = 7.9 Hz, 1H), 4.14-4.05 (m, 1H), 3.74 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.14 (d, *J* = 11.9, 1H), 2.42 (s, 3H), 2.12-2.05 (m, 3H), 1.97 (t, *J* = 10.6 Hz, 1H), 1.64-1.56 (m, 3H), 1.06 (s, 3H), 0.99 (dd, *J* = 12.0, 0.8 Hz, 1H), 0.94 (s, 3H), 0.93-0.90 (m, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 172.1, 143.7, 133.6, 129.6, 127.5, 56.9, 50.4, 43.4, 43.0, 38.5, 31.4, 28.1, 24.7, 21.2, 19.0, 13.5. IR (film): $\tilde{\upsilon}$ = 3296, 3285, 2960, 1645, 1536, 1495, 1464, 1159, 1092, 1030, 993, 774, 661. HRMS (ESI): *m/z*: calcd for $C_{18}H_{29}N_2O_3S$: 353.1893. Found: 353.1898.

***N*-(5,5-Cyclohexyl-1-tosylpiperidin-3-yl)acetamide (8d)**



Following the general procedure of aminoamidation in acetonitrile, compound **8d** was isolated in 74% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.61 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.33 (bs, 1H), 4.11-4.02 (m, 1H), 3.77 (dd, *J* = 11.1, 4.7 Hz, 1H), 3.45 (d, *J* = 11.1 Hz, 1H), 2.42 (s, 3H), 2.06-1.95 (m, 2H), 1.89 (s, 3H), 1.76-1.23 (m, 11H), 0.91 (dd, *J* = 12.7, 11.1 Hz, 1H).^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.7, 144.1, 134.2, 130.1, 127.9, 54.7, 51.3, 43.5, 41.7, 37.7, 34.5, 33.1, 26.8, 23.5, 21.9, 21.7, 21.7. IR (film): $\tilde{\upsilon}$ = 3287, 3060, 2850, 1653, 1541, 1454, 1341, 1310, 1164, 1091, 962, 810, 665.

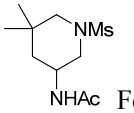
***N*-(1-Tosyl-1,2,3,4-tetrahydroquinolin-3-yl)acetamide (8e) and N-((1-tosylindolin-2-yl)methyl)acetamide (9e)**



Following the general procedure of aminoamidation in acetonitrile, a 1:1 mixture of compounds **8e** and **9e** was isolated in 70% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.68-7.05 (m, 16H), 6.21 (bs, 1H), 5.26 (bs, 1H), 4.35-4.29 (m, 1H), 4.20-4.12 (m, 1H), 4.09-4.01 (m, 1H), 3.61 (dd, *J* = 12.5, 7.1 Hz, 1H), 3.52-3.46 (m, 1H), 3.24-3.17 (m, 1H), 2.84-2.68 (m, 2H), 2.55-2.48 (m, 2H), 2.39 (s, 3H), 2.345 (s, 3H), 1.94 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.6, 169.6, 144.5, 144.2, 140.9, 136.8,

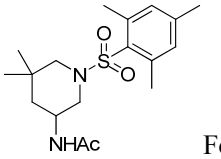
136.4, 134.5, 132.5, 132.0, 129.9, 129.7, 129.6, 128.6, 127.8, 127.0, 126.9, 125.2, 125.1, 124.8, 122.8, 118.1, 61.6, 49.9, 43.7, 42.8, 33.0, 32.3, 23.0, 22.9, 21.2 (One carbon signal is missing due to overlapping). IR (film): $\tilde{\upsilon}$ = 3391, 3298, 3054, 2956, 1655, 1536, 1349, 1164, 1089, 906, 727, 670. HRMS (ESI): *m/z*: calcd for $C_{18}H_{20}N_2O_3SNa$: 367.1086. Found: 367.1084.

***N*-(5,5-Dimethyl-1-(methylsulfonyl)piperidin-3-yl)acetamide (8f)**



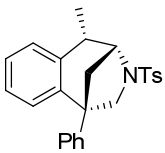
Following the general procedure of aminoamidation in acetonitrile, compound **8f** was isolated in 64% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 5.32 (bs, 1H), 4.06 (sept, *J* = 4.5 Hz, 1H), 3.82 (ddt, *J* = 10.9, 4.5, 1.5 Hz, 1H), 3.21 (dt, *J* = 11.6, 1.6 Hz, 1H), 2.75 (s, 3H), 2.47 (d, *J* = 11.6 Hz, 1H), 2.32 (dd, *J* = 10.9, 9.2 Hz, 1H), 1.91 (s, 3H), 1.67 (ddt, *J* = 12.7, 4.5,1.5 Hz, 1H), 1.16 (dd, *J* = 12.7, 11.1 Hz, 1H), 1.07 (s, 3H). 1.00 (s, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.7, 57.1, 50.6, 44.0, 43.5, 35.8, 32.0, 28.5, 24.9, 23.5. IR (film): $\tilde{\upsilon}$ = 3373, 3269, 2925, 1651, 1547, 1466, 1328, 1151, 968, 817, 713. HRMS (ESI): *m/z*: calcd for $C_{10}H_{20}N_2O_3SNa$: 271.1086. Found: 271.1085.

***N*-(1-(Mesitylsulfonyl)-5,5-dimethylpiperidin-3-yl)acetamide (8g)**



Following the general procedure of aminoamidation in acetonitrile, compound **8g** was isolated in 46% yield; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.98 (s, 2H), 5.38 (bs, 1H), 4.07-3.97 (m, 1H), 3.67 (dd, *J* = 1.1, 4.6 Hz, 1H), 3.04 (d, *J* = 12.1 Hz, 1H), 2.60 (s, 6H), 2.57-2.51 (m, 2H), 2.30 (s, 3H), 2.28-2.27 (m, 1H), 1.89 (s, 3H), 1.1 (dd, *J* = 11.6, 0.9 Hz, 1H), 0.94 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.2, 142.8, 140.3, 131.9, 131.9, 131.8, 55.4, 48.4, 43.4, 43.3, 31.5, 28.3, 24.4, 22.7, 20.7. IR (film): $\tilde{\upsilon}$ = 3272. 2955, 2851, 1656, 1603, 1545, 1311, 1182, 1152, 966, 696. HRMS (ESI): *m/z*: calcd for $C_{18}H_{28}N_2O_3SNa$: 375.1712. Found: 375.1714.

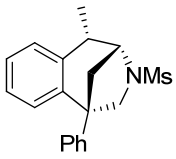
Product 10k



Following the general procedure of aminoarylation, compound **10k** was isolated in 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.5 Hz, 2H), 7.34-7.14 (m, 9H), 6.92 (t, *J* = 8.5 Hz, 1H), 6.38 (dd, *J* = 7.9, 1.1 Hz, 1H), 4.34 (dd, *J* = 6.3, 3.1 Hz,

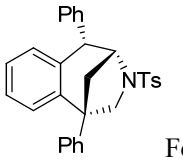
1H), 3.88 (dd, *J* = 8.4, 1.1 Hz, 1H), 3.59 (d, *J* = 8.4 Hz, 1H), 3.24 (td, *J* = 6.3, 3.1 Hz, 1H), 2.44- 2.39 (m, 1H), 2.38 (s, 3H), 1.61 (d, *J* = 7.0 Hz, 3H), 1.60-1.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 143.5, 143.0, 138.4, 134.5, 129.8, 127.9, 127.6, 127.5, 127.3, 127.1, 126.4, 125.9, 63.0, 61.4, 51.7, 40.8, 40.8, 21.5, 19.1. (One aromatic carbon signal is missing due to overlapping). IR (film): $\tilde{\upsilon}$ = 3060, 2969, 1445, 1338, 1264, 1161, 1090, 1027, 768, 734, 700, 662. MS (ESI): *m/z*: calcd for $C_{25}H_{25}NO_2SNa$: 426.2. Found: 426.2.

Product 10l



Following the general procedure of aminoarylation, compound **10l** was isolated in 68% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.16 (m, 7H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.48 (d, *J* = 7.4 Hz, 1H), 4.33 (dd, *J* = 6.4, 3.1 Hz, 1H), 3.90 (d, *J* = 8.4 Hz, 1H), 3.85 (d, *J* = 8.4 Hz, 1H), 3.27 (td, *J* = 6.4, 3.1 Hz, 1H), 2.85 (s, 3H), 2.66 (d, *J* = 11.1 Hz, 1H), 2.25 (dd, *J* = 11.1, 6.4 Hz, 1H), 1.52 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.6, 142.7, 138.1, 127.9, 127.7, 127.4, 127.3, 126.4, 126.1, 62.7, 61.8, 52.0, 41.4, 40.7, 35.0, 19.1. (One aromatic carbon signal is missing due to overlapping). IR (film): $\tilde{\upsilon}$ = 2971, 2932, 1735, 1497, 1483, 1445, 1416, 1333, 1264, 1200, 1153, 1045, 1038, 962, 750, 733, 700. HRMS (ESI): *m/z*: calcd for $C_{19}H_{21}NO_2SNa$: 350.1185 Found: 350.1182.

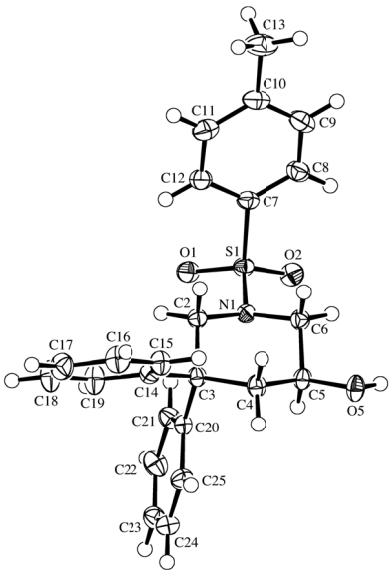
Product 10m



Following the general procedure of aminoarylation, compound **10m** was isolated in 42% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.8 Hz, 2H), 7.43-7.04 (m, 15H), 6.60 (d, *J* = 7.8 Hz, 1H), 4.80 (d, *J* = 2.7 Hz, 1H), 4.38 (dd, *J* = 6.2, 2.7 Hz, 1H), 4.00 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.61 (d, *J* = 8.0 Hz, 1H), 2.55 (d, *J* = 11.1 Hz, 1H), 2.40 (s, 3H), 1.46 (dd, *J* = 11.1, 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5, 143.4, 143.2, 142.3, 135.3, 135.1, 131.3, 129.8, 129.4, 128.6, 127.6, 127.4, 127.3, 127.1, 126.8, 126.7, 126.6, 63.8, 60.3, 53.9, 51.2, 35.0, 21.5. (One aromatic carbon signal is missing due to overlapping). IR (film): $\tilde{\upsilon}$ = 3060, 3026, 2922, 1598, 1493, 1447, 1340, 1163, 1091, 910, 728, 700, 665. HRMS (ESI): *m/z*: calcd for $C_{30}H_{27}NO_2SNa$: 488.1654. Found: 488.1653.

4.5 Crystallography datas

5,5-Diphenyl-1-tosylpiperidin-3-ol (2b) (CCD4791449)

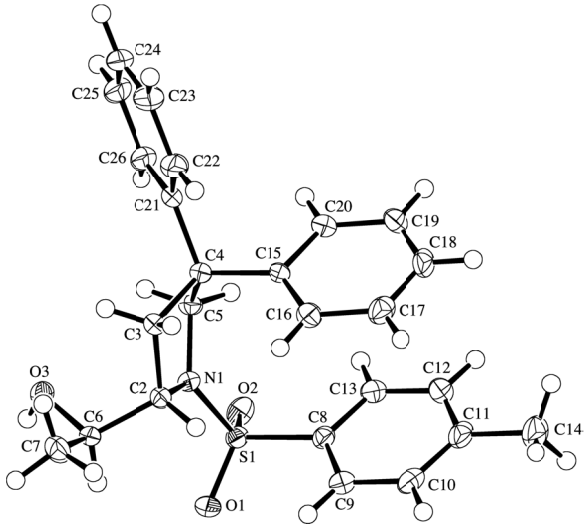


Crystallised from	CH_2Cl_2
Empirical formula	$C_{24}H_{25}NO_3S$
Formula weight [g mol^{-1}]	407.53
Crystal colour, habit	colourless, prism
Crystal dimensions [mm]	0.15 × 0.20 × 0.25
Temperature [K]	160(1)
Crystal system	monoclinic
Space group	$P2_1/n$ (#14)
Z	4
Reflections for cell determination	31459
2θ range for cell determination [°]	4 – 60
Unit cell parameters a [Å]	9.8084(1)
b [Å]	11.3162(2)

c [Å]	18.7935(2)
α [°]	90
β [°]	97.5697(8)
γ [°]	90
V [Å^3]	2067.78(5)
F(000)	864
D_x [g cm^{-3}]	1.309
μ(Mo $K\alpha$) [mm^{-1}]	0.182
Scan type	ϕ and ω
$2\theta_{(max)}$ [°]	60
Transmission factors (min; max)	0.839; 0.974
Total reflections measured	56692
Symmetry independent reflections	6017
R_{int}	0.064
Reflections with $I > 2\sigma(I)$	4754
Reflections used in refinement	6017
Parameters refined	268
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0420
$wR(F^2)$ (all data)	0.1094
Weights: $w = [\sigma^2(F_o^2) + (0.0480P)^2 + 0.8483P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$	
Goodness of fit	1.033
Secondary extinction coefficient	0.005(1)
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.29; -0.41

$\sigma(d_{(C-C)})$ [Å]	0.002

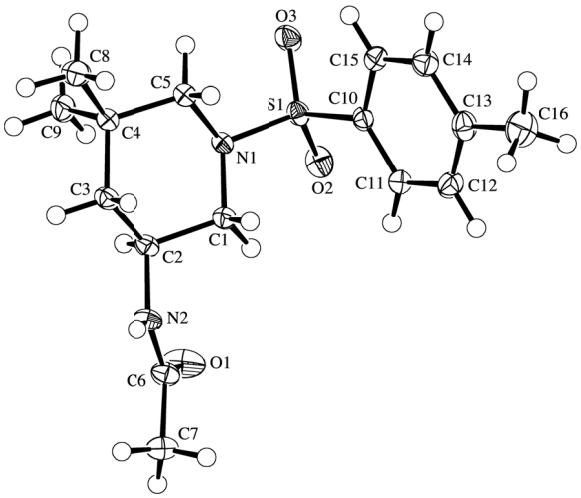
(±)(*S*)-1-((*R*)-4,4-diphenyl-1-tosylpyrrolidin-2-yl)ethanol (3k) (CCDC791448)



Crystallised from	CH_2Cl_2
Empirical formula	$C_{25}H_{27}NO_3S$
Formula weight [g mol^{-1}]	421.55
Crystal colour, habit	colourless, plate
Crystal dimensions [mm]	0.04 × 0.08 × 0.20
Temperature [K]	160(1)
Crystal system	monoclinic
Space group	$P2_1/c$ (#14)
Z	4
Reflections for cell determination	22
2θ range for cell determination [°]	6−57
Unit cell parameters a [Å]	14.1789(2)
b [Å]	6.0686(1)
c [Å]	25.1361(4)

α [°]	90
β [°]	100.155(2)
γ [°]	90
V [Å^3]	2128.97(6)
F(000)	896
D_x [g cm^{-3}]	1.315
μ(Mo $K\alpha$) [mm^{-1}]	0.179
Scan type	ω
$2\theta_{(max)}$ [°]	57
Total reflections measured	18564
Symmetry independent reflections	4690
R_{int}	0.027
Reflections with $I > 2\sigma(I)$	3725
Reflections used in refinement	4690
Parameters refined	277
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0396
$wR(F^2)$ (all data)	0.1118
Weights:	$w = [\sigma^2(F_o^2) + (0.0612P)^2 + 0.7760P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness of fit	1.047
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.38; -0.45
$\sigma(d_{(C-C)})$ [Å]	0.002 – 0.003

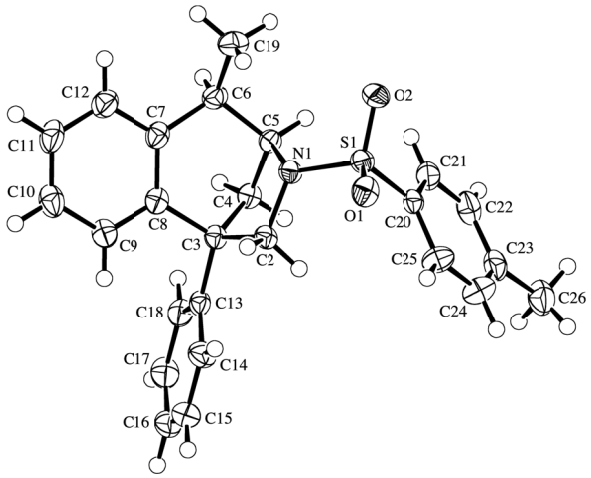
***N*-(5,5-Dimethyl-1-tosylpiperidin-3-yl)acetamide (8c)** (CCDC791447)



Crystallised from		CH_2Cl_2
Empirical formula		$C_{16}H_{24}N_2O_3S$
Formula weight [g mol^{-1}]		324.44
Crystal colour, habit		colourless, prism
Crystal dimensions [mm]		0.18 × 0.20 × 0.32
Temperature [K]		160(1)
Crystal system		monoclinic
Space group		$P2_1/c$ (#14)
Z		4
Reflections for cell determination		9984
2θ range for cell determination [°]		5.6 – 64.5
Unit cell parameters	a [Å]	9.1812(1)
	b [Å]	9.2307(1)
	c [Å]	19.7108(2)
	α [°]	90
	β [°]	95.317(1)
	γ [°]	90

V [Å^3]	1663.29(5)
F(000)	696
D_x [g cm^{-3}]	1.295
μ(Mo $K\alpha$) [mm^{-1}]	0.209
Scan type	ω
$2\theta_{(max)}$ [°]	64.6
Total reflections measured	21962
Symmetry independent reflections	5514
R_{int}	0.026
Reflections with $I > 2\sigma(I)$	4501
Reflections used in refinement	5514
Parameters refined	207
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0394
$wR(F^2)$ (all data)	0.1056
Weights:	$w = [\sigma^2(F_o^2) + (0.0414P)^2 + 0.8187P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness of fit	1.045
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.40; -0.43
$\sigma(d_{(C-C)})$ [Å]	0.002

Product 10k (CCDC791446)



Crystallised from	CH_2Cl_2
Empirical formula	$C_{25}H_{25}NO_2S$
Formula weight [g mol^{-1}]	403.54
Crystal colour, habit	colourless, prism
Crystal dimensions [mm]	0.08 × 0.20 × 0.20
Temperature [K]	160(1)
Crystal system	monoclinic
Space group	$P2_1/n$ (#14)
Z	4
Reflections for cell determination	7545
2θ range for cell determination [°]	5 − 57
Unit cell parameters a [Å]	8.1673(2)
b [Å]	13.9858(3)
c [Å]	18.4430(4)
α [°]	90
β [°]	102.118(2)
γ [°]	90

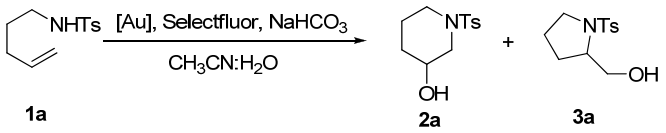
V [Å^3]	2059.72(8)
F(000)	856
D_x [g cm^{-3}]	1.301
μ(Mo $K\alpha$) [mm^{-1}]	0.178
Scan type	ω
$2\theta_{(max)}$ [°]	57
Total reflections measured	17033
Symmetry independent reflections	4515
R_{int}	0.026
Reflections with $I > 2\sigma(I)$	3673
Reflections used in refinement	4515
Parameters refined	264
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0431
$wR(F^2)$ *(all data)*	0.1181
Weights:	$w = [\sigma^2(F_o^2) + (0.0496P)^2 + 1.1024P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$
Goodness of fit	1.059
Final Δ_{max}/σ	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.30; -0.35
$\sigma(d_{(C-C)})$ [Å]	0.002 – 0.003

The abovementioned CCDC numbers contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via *www.ccdc.cam.ac.uk/data_request/cif*.

4.6 Supplementary data

4.6.1 Further optimization reactions (cont. Table 1)[a]

Table 1. Optimization of the reaction conditions (Cont.)



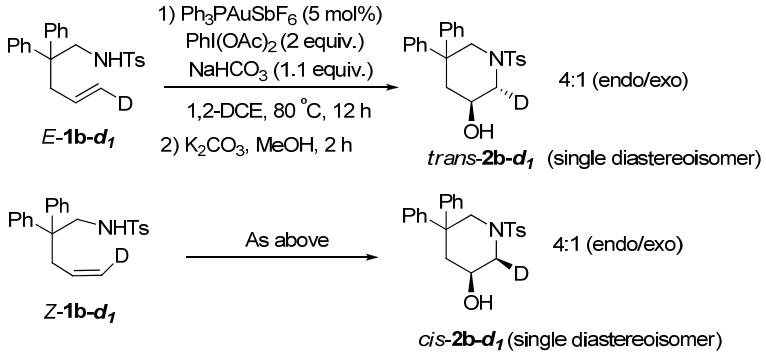
1a **2a** **3a**

Entry	Modification in the Reaction Conditions[a]	Conv.[b] (%)	**2a**:**3a** ratio, (Yield, %)
1	$Ph_3PAuSbF_6$, 40 ºC, 12 h	0	-
2	$Ph_3PAuSbF_6$, 60 ºC, 12h	50	n.d.
3	$Ph_3PAuSbF_6$, 80 ºC, 2 h, no water	100	decomposition
	$Ph_3PAuSbF_6$, 80 ºC, 2 h, $PhI(OAc)_2$ instead of Selectfluor	0	-
5	$Ph_3PAuSbF_6$, 80 ºC, 2 h, TEMPO instead of Selectfluor	0	-
6	$Ph_3PAuSbF_6$, 80 ºC, 2 h, with $PhNO_2$ as additive	60	n.d.
7	$Ph_3PAuSbF_6$, 80 ºC, 2 h, MeCN:AcOH	0	-
8	CuI or $Cu(OTf)_2$	100	decomposition
9	$(t\text{Bu})_3PAuNTf_2$	0	-
10	No Gold, TFA (5%), no base, 20 h	0	-
11	No Gold, CF_3SO_3H (2%), no base, 20 h	0	-
12	No Gold, $AgSbF_6$ (5%)	0	-
13	$[Rh(COD)]_2$ SbF_6 (5%), 20 h	0	-
14	$Ph_3PAuSbF_6$, with NaH, 3 h	83[e]	-

[a] Standard conditions: [Au]: 5mol%, Selectfluor (2 equiv), $NaHCO_3$ (1.1 equiv), $CH_3CN:H_2O$ (20:1), 0.02 M, 80 ºC, 12h. [b] Checked by GC-MS. [c] n.d.: not determined. [d] Isolated yield for major regioisomer.[e] Remaining 17% is the aminoamidation product.

4.6.2 Deuterium labeling studies for the aminoacetoxylation reaction

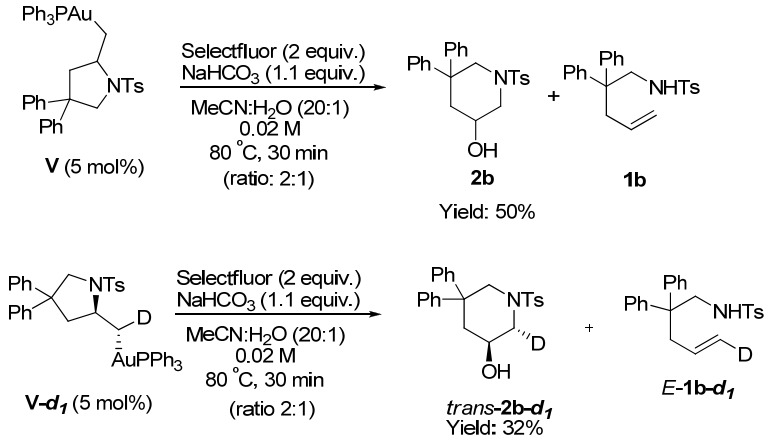
Scheme 6. Deuterium labeling experiments



4.6.3 Mechanistic studies using alkylgold complexes as starting materials

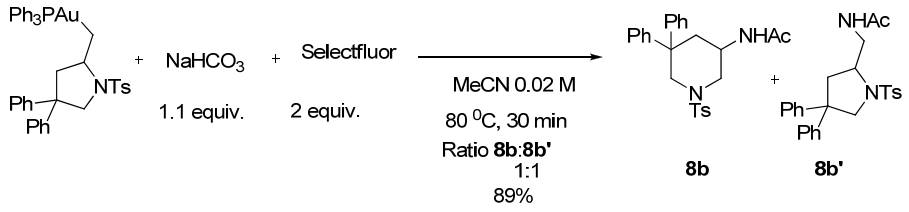
A mixture of alkylgold complex (**V**[10] or **V-*d*$_1$**, 0.05 equiv.), Selectfluor (2 equiv.) and $NaHCO_3$ (1 equiv.) was dissolved in MeCN:H_2O (20:1, 0.02 M). The reaction was stirred at 80 °C and was monitored by TLC. Upon consumption of **V**, the mixture was diluted with DCM (5 ml) and water (2 ml) was added. The mixture was extracted with DCM (3 x 5 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified through silica gel flash column chromatography (Hexane/EtOAc = 4/1) to yield the desired aminoalcohols **2b** and *trans*-**2b-*d*$_1$**.

Scheme 7. Aminohydroxylation from alkylgold(I) complexes



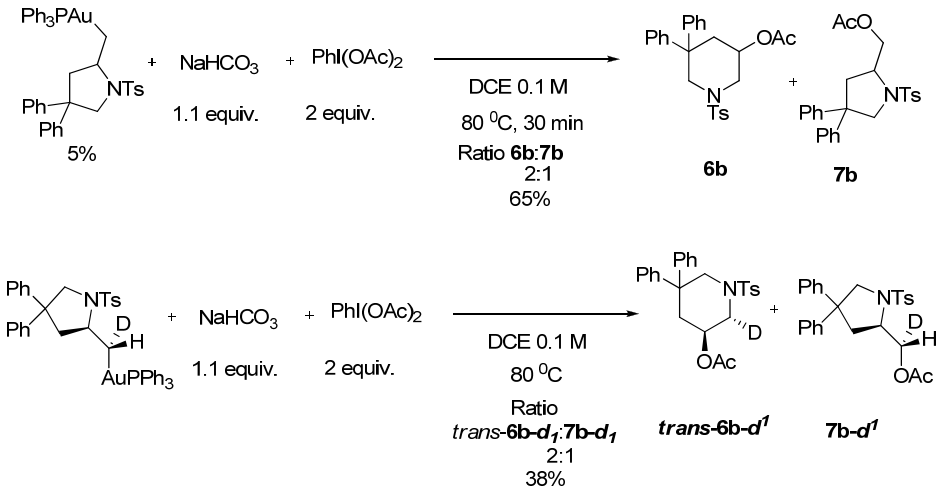
Moreover, when a mixture of alkylgold complex **V** (0.05 equiv.), Selectfluor (2 equiv.) and $NaHCO_3$ (1 equiv.) was dissolved in MeCN (0.1 M) and stirred at 80 °C, the reaction afforded the aminoamidate products as a regioisomeric mixture in a ratio 1:1.

Scheme 8. Aminoamidation from alkylgold(I) complexes



In addition, a mixture of alkylgold complex (**V** or **V**-d_1, 0.05 equiv.), $PhI(OAc)_2$ (2 equiv.) and $NaHCO_3$ (1 equiv.) was dissolved in DCE (0.1 M). The reaction was stirred at 80 ^oC and was monitored by TLC. Upon consumption of the starting material, the mixture was diluted with DCM (5 ml) and water (2 ml) was added. The mixture was filter under a pad of Celite and the solvent was evaporated under reduced pressure and the residue was purified through silica gel flash column chromatography (Hexane/EtOAc = 10/1) to yield a mixture of aminoacetates **6b** and **7b** in 2:1 ratio and *trans*-**6b**-d_1 and **7b**-d_1 in 2:1 ratio.

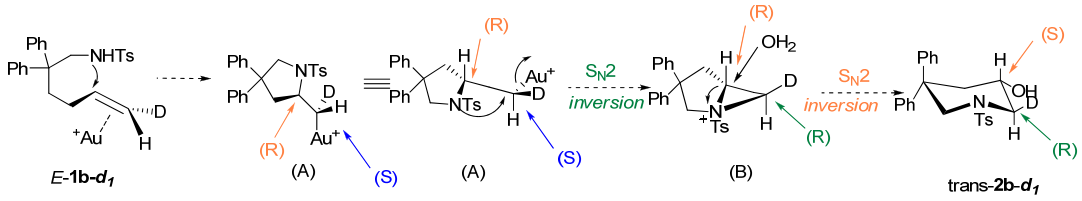
Scheme 9. Aminoacetoxylation form alkylgold(I) complexes



Michael has recently invoked aziridine intermediates formed from intermediate (**A**) to explain the formation of *6-endo* products in a Pd-catalyzed alkoxyamination.[11] A similar pathway could be operating in this reaction. The deuterium labelling experiments performed with **1b** and summarized in Scheme 3 are compatible this mechanistic hypothesis: (Scheme 10) if *E*-**1b**-d_1 is activated with gold, intermediate **A** is generated. Upon gold departure via intramolecular nucleophilic attack of the *N*-moiety, aziridine **B** would be formed and the attack of the external nucleophile (water, acetic acid, alcohol) would occur with inversion of the configuration at the C-center, so that in the final product the nucleophile and the

deuterium atom should be *"trans"* to give *trans*-**2b**-d_1, which is in agreement with the observed product distribution, where *E*-**1b**-d_1 affords *trans*-**2b**-d_1 in 79% as a single diastereoisomer (Scheme 3).

Scheme 10. Towards the mechanism in the gold catalyzed difunctionalization of alkenes



4.7 References

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CHAPTER 5

Domino Gold-Catalyzed Rearrangement and Fluorination of Propargyl Acetates

CHAPTER 5

Domino Gold-Catalyzed Rearrangement and Fluorination of Propargyl Acetates

Teresa de Haro and Cristina Nevado*

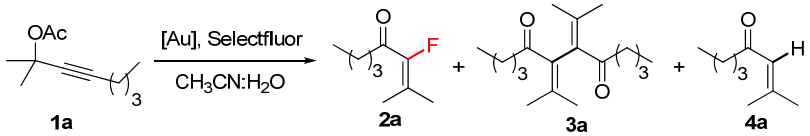
(*Chem. Commun.* **2011**, *47*, 248)

The efficient formation of C-F bonds represents a major challenge in organic and organometallic chemistry.[1] In recent years catalytic methods have been developed, usually involving electrophilic fluorinating reagents and/or specific directing groups in the substrate with Pd as catalyst.[2] Gold-complexes have also been used in catalytic fluorinations, as independently reported by the groups of Sadighi and Governeur. While Sadighi´s group has focused on the hydrofluorination of alkynes,[3] Governeur has used the fluorodeauration of vinyl gold species to create new Csp^2-F bonds, although the competitive formation of Csp^2-H bonds could not be avoided.[4] Additionally, vinyl-gold species have proved to efficiently form Csp^2-Br and Csp^2-I bonds in a catalytic fashion.[5] Based on our previous experience in the gold-catalyzed rearrangement of propargyl acetates,[6] we decided to explore the reactivity of these motives in the presence of different fluorinating agents combining the "alkynophilicity" of gold(I) complexes with a redox gold(I)/gold(III) catalytic cycle to establish a new C-F bond upon acyloxy migration to give α-fluoroenones. Despite their synthetic potential as Michael acceptors or as precursors of peptidomimetics,[7a] only few methods to prepare α-fluoroenones are known.[7b-c]

Acetate **1a** was prepared and used as benchmark substrate to find the optimal reaction conditions for such tandem process (Table 1). The reaction of **1a** in the presence of commercially available Ph_3PAuCl (5 mol%) and Selecfluor (2 equiv.) afforded a 4:2:1 mixture of the desired α-fluoroenone (**2a**), dimer (**3a**)[8] and the corresponding α,β-unsaturated ketone **4a** (Table 1, entry 1). When $Ph_3PAuNTf_2$ was used as catalyst (Table 1, entry 2), the amount of **4a** was significantly reduced. In our recent study on the gold-catalyzed ethynylation of arenes,[9] we experienced that the presence of base prevented the undesired homocoupling of the aromatic counterpart. Thus, different bases such as potassium carbonate, magnesium oxide and sodium bicarbonate were used as additives in the reaction hoping to minimize the formation of **3a** and **4a** (Table 1, entries 3-5). $NaHCO_3$ provided the best result, with complete conversion of the starting material into **2a** as major reaction product. Next, we

decided to further explore the influence of the gold pre-catalyst in this process. Complexes such as $Ph_3PAuSbF_6$ and $(PhO)_3PAuSbF_6$ were used revealing the key role of the counteranion (Table 1, entries 6 and 7). Both catalysts favored the protonolysis of the vinyl Csp^2-Au bond delivering **4a** as the only reaction product. We also checked the influence of the temperature and number of equivalents of fluorinating agent. The reaction with $Ph_3PAuNTf_2$ as catalyst at 60 ºC afforded, after 45 min, the best ratio on the desired product **2a** although complete conversion could not be obtained (Table 1, entry 8). Using just one equivalent of Selectfluor, a similar result was obtained (Table 1, entry 9). At this stage, we reasoned that the stability of the Csp^2-Au bond could play a key role to avoid the competitive protonation event, and that the bulkiness of the ligand could also influence the homocoupling reaction. Thus, we decided to use a bulky *N*-heterocyclic ligand such as 1,3-bis(2,6-diiso-propylphenyl)-imidazol-2-ylide, which is also known to be a strong σ-donor and a weak π-acceptor. To our delight, $IPrAuNTf_2$ delivered the fluorinated product **2a** with complete conversion and excellent selectivity (Table 1, entry 10).

Table 1. Optimization of the reaction conditions[a]



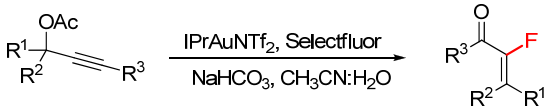
Entry	Catalyst	Additive	Conversion (%)	Ratio[b]
1	Ph_3PAuCl	-	100	60:26:13
2	$Ph_3PAuNTf_2$	-	100	54:45:1
3	$Ph_3PAuNTf_2$	K_2CO_3 (1 equiv.)	0	-
4	$Ph_3PAuNTf_2$	MgO (1 equiv.)	55	77:12:11
5	$Ph_3PAuNTf_2$	$NaHCO_3$ (1 equiv.)	100	75:13:12
6	$Ph_3PAuSbF_6$	$NaHCO_3$ (1 eq.)	100	0:0:100
7	$(PhO)_3PAuSbF_6$	$NaHCO_3$ (1 equiv.)	61	0:0:100
8	$Ph_3PAuNTf_2$	$NaHCO_3$ (1 equiv.), 60ºC	60	92:0:8
9	$Ph_3PAuNTf_2$	$NaHCO_3$ (1 equiv.), Selecfluor (1 equiv.)	64	88:6:6
10	**$IPrAuNTf_2$**	**$NaHCO_3$ (1 equiv.)**	**100**	**99:<1:<1**

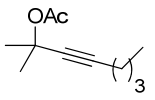
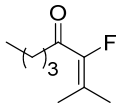
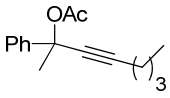
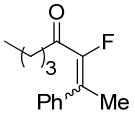
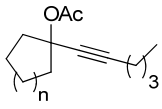
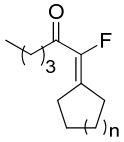
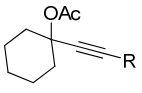
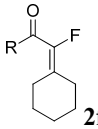
[a] Standard reaction conditions: [Au(I)] (5 mol%), Selectfluor (2 equiv.), 20:1 $CH_3CN:H_2O$ as solvent (substrate concentration 0.02 M), 80 ºC, 20 min. [b] Determined by ^{1}H-NMR with TMSCl as internal standard.

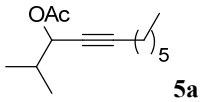
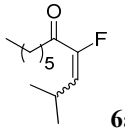
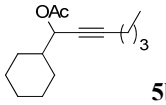
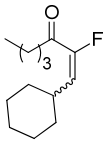
We then decided explored the scope of this transformation (Table 2). Under the previously optimized conditions, **1a** afforded the desired fluorinated product (**2a**) in 77% isolated yield (Table 2, entry 1). The substrate derived from acetophenone (**1b**) delivered the corresponding

α-fluoroenone **2b** in 84% yield as a 1.5:1 mixture of *E:Z* isomers (Table 2, entry 2).[10] Substrates derived from cyclic ketones such as **1c**, **1d** and **1e** reacted smoothly in the presence of $IPrAuNTf_2$ delivering the corresponding fluorinated products (**2c-e**) in 82, 71 and 87% yield respectively (Table 2, entries 3-5). We also explored the substitution pattern in the alkyne moiety. A longer alkylic chain (**1f**) was well accommodated under these conditions (Table 2, entry 6). The presence of a cyclopropyl group (**1g**) was also tolerated although partial decomposition of **2g** could not be avoided during the purification process (Table 2, entry 7). Phenyl substituted alkyne **1h** smoothly reacted to give fluorinated ketone **2h** in 81% yield (Table 2, entry 8). Secondary acetates (**5a**, **5b**) reacted efficiently by increasing the concentration and the reaction time (Table 2, entries 9 and 10). In these cases, the *E* isomer was the major product detected in the reaction mixtures.

Table 2. Study of the reaction scope[a]

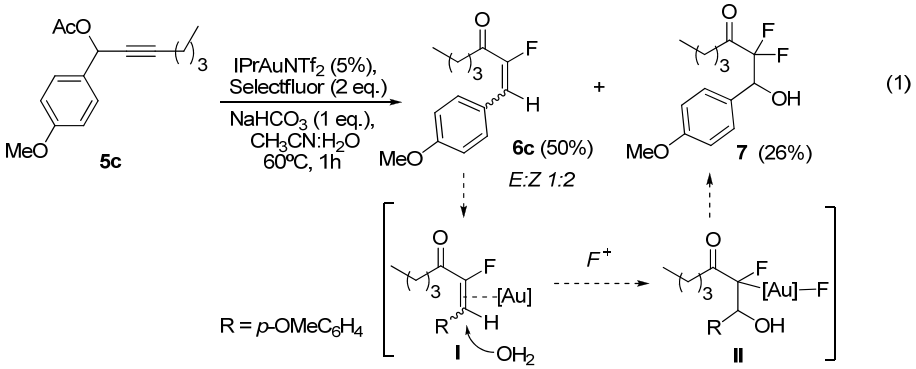


Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **2a**	77
2	 **1b**	 **2b**	84[c]
3	 **1c** (n = 1)	 **2c** (n = 1)	82
4	**1d** (n = 2)	**2d** (n = 2)	71
5	**1e** (n = 3)	**2e** (n = 3)	87
6	 **1f**	 **2f** (R = *n*Hex)	79
7	**1g** (R =1-*cyclopropyl*)	**2g** (R =1-*cyclopropyl*)	57

8	**1h** (R = Ph)	**2h** (R = Ph)	81
9	 **5a**	 **6a**	71 [d],[e]
10	 **5b**	 **6b**	72[d],[e]

[a] Standard reaction conditions: $IPrAuNTf_2$ (5 mol%), Selectfluor (2 eq.), 20:1 $CH_3CN:H_2O$ as solvent (substrate concentration 0.02 M), 80 ºC, 20 min. [b] Isolated yield after column chromatography. [c] 1.5:1 *E:Z* ratio. [d] As standard conditions but stirred for 2 h, substrate concentration 0.1M. [e] 4:1 *E:Z* ratio.

Interestingly, *p*-methoxyphenyl substituted propargyl acetate **5c** afforded not only the isomeric *α*-fluoroenones **6c** (2:1 *Z:E* ratio), but also bis-fluorinated compound **7** isolated in 26% yield (eq. 1).[4,11] Reactivation of the double bond in **6c** by gold(I) or gold(III) present in the reaction mixture could trigger the nucleophilic attack of water (**I**), followed by fluorination at the C_α of the ketone (**II**) through the Csp^3-Au bond.

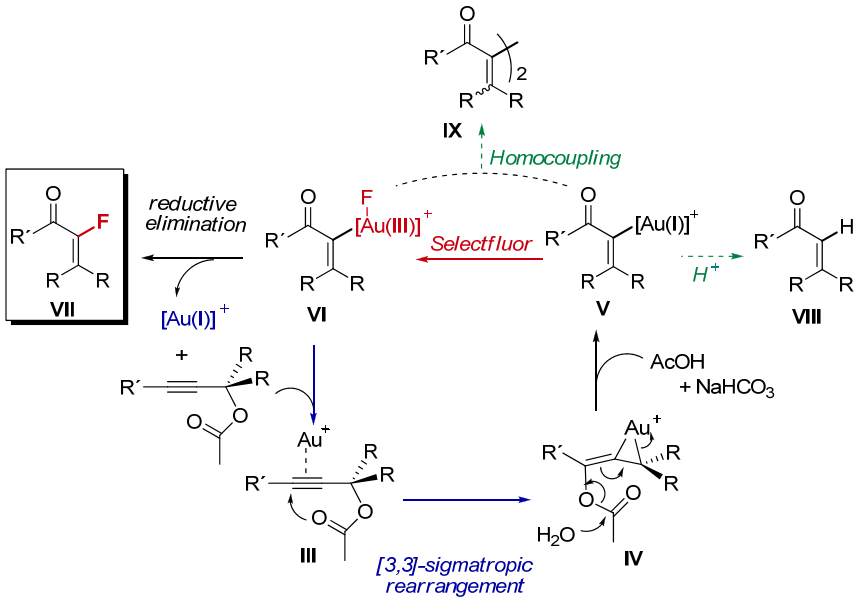


(1)

Our mechanistic proposal for the formation of *α*-fluoroenones has been outlined in Scheme 1. Upon gold coordination, the complex **III** undergoes a [3,3]-sigmatropic rearrangement of the acyloxy moiety affording allene **IV**, which according to previously reported DFT calculations, features gold coordinated to the external double bond of the allene.[12] Hydrolysis of the acetoxy moiety in the aqueous media will deliver vinyl-gold(I) species **V** while releasing acetic acid, which can be neutralized in the presence of base ($NaHCO_3$). In the presence of a strong oxidant such as Selectfluor, oxidation of gold(I) to gold(III) can occurr affording complex **VI**.[13] Reductive elimination in **VI** will deliver the new Csp^2-F bond and the observed *α*-fluorenones **VII**.[14] As competing pathways, protonolysis of **V** could deliver *α,β*-unsaturated ketones (**VIII**), or transmetalation between **V** and **VI** could afford the homocoupling products **IX** (Scheme 1, green pathways).[8] Under the standard reaction conditions, *E*-**6a**,**6b** did not isomerized to the

thermodynamically more stable Z-isomers,[15] thus indicating that the step defining the stereochemistry of the enone must be under kinetic control.

Scheme 1. Proposed Mechanistic Pathway



In summary, we present here a novel and efficient method to synthetize α-fluoroenones based on a domino gold-catalyzed process starting from easily available propargyl acetates. The known tendency of gold(I)-complexes to activate alkynes triggers the 1,3-migration of the acyloxy moiety onto the triple bond delivering vinyl-gold(I) intermediates, which can be oxidized in the presence of Selectfluor to form gold(III) species prone to reductive elimination to give Csp^2-F bonds. Further studies on the reaction mechanism and applications of this method to other substrates are currently ongoing.

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[10] See Chapter V: Experimental Section, Supplementary data.

[11] Under the standard reaction conditions **6c** was quantitatively transformed in **7**.

[12] For an in depth computational study on similar intermediates, see: (a) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 718; (b) V. Gandon, G. Lemière, A. Hours, L. Fensterbank, M. Malacria, *Angew. Chem. Int. Ed.* **2008**, *47*, 7534; (c) Garayalde, D.; Gómez-Bengoa, E.; Huang, X.; Göeke, A.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 4720.

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[14] Fluorodeauration of the vinylic Csp^2-Au(I) bond in the presence of "F^+" cannot be ruled out.

[15] Semiempirical calculations (PM3 level), showed an energy difference between the *E* and *Z* isomers ≈ 5 kcal/mol, with *Z* isomer being the thermodynamically more stable

Chapter 5

Experimental Section

Table of Contents

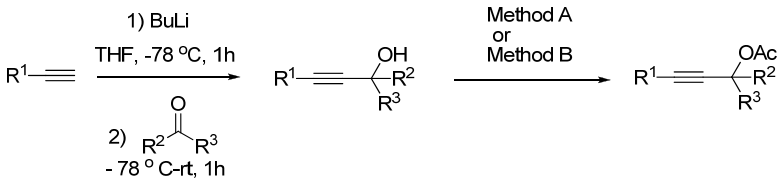
5.1 General information

NMR spectra were recorded on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual ^{1}H and ^{13}C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution electrospray ionization and electronic impact mass spectrometry was performed on a Finnigan MAT 900 (Thermo Finnigan, San Jose, CA; USA) doublefocusing magnetic sector mass spectrometer. Ten spectra were acquired. A mass accuracy ≤ 2 ppm was obtained in the peak matching acquisition mode by using a solution containing 2 <l PEG200, 2 <l PPG450, and 1.5 mg NaOAc (all obtained from Sigma-Aldrich, CH-Buchs) dissolved in 100ml MeOH (HPLC Supra grade, Scharlau, E-Barcelona) as internal standard. GC-MS analysis was done on a Finnigan Voyager GC8000 Top.

Materials and Methods: Unless otherwise stated, starting materials were purchased from Aldrich and/or Fluka. All reagents were used as received. $IPrAuNTf_2$ was prepared according to previously reported procedures.[1] Solvents were purchased in HPLC quality, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Unless otherwise stated, reactions were not run under inert atmosphere. Conversion was monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. Flash column chromatography was performed over silica gel (230-400 mesh). The determination of the E/Z ratios for the α-fluoroenones derived of secondary acetates was done by ^{1}H-NMR of the crude reaction mixtures.

5.2 Preparation and characterization of starting materials

5.2.1 General procedures



A solution of the corresponding alkyne (1.0 equiv.) in anhydrous THF (0.3 M) was treated with *n*BuLi (1.05 equiv.) at -78°C for 1 h. The corresponding aldehyde or ketone was added dropwise. The resulting reaction mixture was stirred at -78ºC for 30 min and then warmed up to rt for another 30 min. It was quenched with saturated NH_4Cl (aq. sol.) and extracted with ether. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated

under reduced pressure. The residue was purified by column chromatography if needed. The propargylic alcohols were transformed into the corresponding propargylic acetates using two different reaction conditions.

Method A:

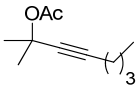
Propargylic alcohol (1 equiv.) was dissolved in CH_2Cl_2 (0.1 M). DMAP (0.05 equiv.), Et_3N (2 equiv.) and Ac_2O (1.5 equiv.) were sequentially added. The resulting mixture was stirred overnight. The solvent was evaporated and the residue was purified by column chromatography on silica gel.

Method B:

Propargylic alcohol (1 equiv.) was stirred with Ac_2O (1.5 equiv.) neat at rt for 30 min in the presence of $Mg(ClO_4)_2$ (0.01 equiv.). The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and the organic solvent was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Hexane:EtOAc 40:1).[2]

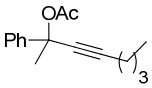
5.2.2 Characterizations of starting materials

2-Methyloct-3-yn-2-yl acetate (1a)[3]



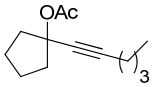
Propargyl acetate **1a** was obtained according to Method B. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19 (t, J = 6.8 Hz, 2H), 2.0 (s, 3H), 1.63 (s, 6H), 1.50-1.42 (m, 2H), 1.41-1.33 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 84.6, 81.3, 72.6, 30.6, 29.3, 22.1, 21.9, 18.4, 13.6.

1-(Hex-1-ynyl)cycloheptyl acetate (1b)[4]



Propargyl acetate **1b** was obtained according to Method A. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49-7.46 (m, 2H), 7.27-7.23 (m, 2H), 7.19-7.16 (m, 1H), 2.23 (t, J = 6.9 Hz, 2H), 1.96 (s, 3H), 1.77 (s, 3H), 1.51–1.45 (m, 2H), 1.41–1.33 (m, 2H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 143.9, 128.8, 128.2, 125.6, 88.7, 80.2, 76.7, 33.0, 31.2, 22.6, 22.5, 19.2, 14.2.

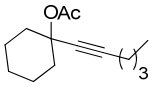
1-(Hex-1-ynyl)cyclopentyl acetate (1c)[3]



Propargyl acetate **1c** was obtained according to Method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.22–2.15 (m, 4H), 2.12–2.04 (m, 2H), 2.02 (s, 3H), 1.74–1.70 (m, 4H), 1.50–

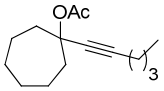
1.44 (m, 2H), 1.43–1.35 (m, 2H), 0.90 (t, J = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 85.8, 81.6, 81.2, 41.1, 31.3, 23.7, 22.5, 22.4, 19.0, 14.2

1-(Hex-1-ynyl)cyclohexyl acetate (1d)[3]



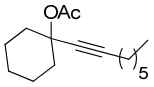
Propargyl acetate **1d** was obtained according to Method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.2 (t, J = 7.2 Hz, 2H), 2.11–2.06 (m, 2H), 2.03 (s, 3H), 1.84–1.77 (m, 2H), 1.63–1.29 (m, 10H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 87.4, 80.7, 76.7, 37.9, 31.4, 25.8, 23.4, 22.7, 22.5, 19.1, 14.2.

1-(Hex-1-ynyl)cycloheptyl acetate (1e)[3]



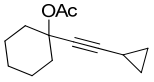
Propargyl acetate **1e** was obtained according to Method A. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.24–2.17 (m, 4H), 2.06–2.04 (m, 2H), 2.01 (s, 3H), 1.57–1.37 (m, 12H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 86.9, 82.1, 80.2, 41.1, 31.4, 28.8, 22.9, 22.8, 22.5, 19.1, 14.2.

1-(Oct-1-ynyl)cyclohexyl acetate (1f)



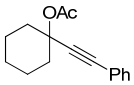
Propargyl acetate **1f** was obtained according Method A. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13 (t, J = 7.1 Hz, 2H), 2.00-1.97 (m, 2H), 1.93 (s, 3H), 1.70 (m, 2H), 1.53-1.48 (m, 4H), 1.44-1.39 (m, 3H), 1.30-1.18 (m, 7H), 0.79 (t, J = 6.9 Hz, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 87.5, 80.7, 76.7, 38.0, 31.9, 29.3, 29.1, 25.9, 23.4, 23.1, 22.7, 19.4, 14.6. IR (film): $\tilde{\upsilon}$ = 2932, 2858, 1744, 1447, 1365, 1300, 1263, 1227, 1184, 1130, 1019, 957, 914, 840 cm^{-1}. HRMS (ESI): *m/z*: calcd for $C_{16}H_{26}O_2Na$: 273.1825. Found: 273.1825.

1-(Cyclopropylethynyl)cyclohexyl acetate (1g)



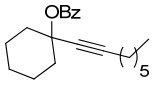
Propargyl acetate **1g** was obtained according to Method A. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97-1.94 (m, 2H), 1.92 (s, 3H), 1.72 (m, 2H), 1.52-1.36 (m, 5H), 1.20-1.17 (m, 2H), 0.69-0.65 (m, 2H), 0.60-0.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 90.6, 76.6, 75.8, 37.9, 25.8, 23.3, 22.7, 9.0, 0.2. IR (film): $\tilde{\upsilon}$ = 2935, 2859, 2359, 2239, 1741, 1447, 1365, 1298, 1264, 1225, 1175, 1132, 1020, 963, 913, 888 cm^{-1}. HRMS (ESI): *m/z*: calcd for $C_{13}H_{18}O_2Na$: 229.1199. Found: 229.1198

1-(2-Phenylethynyl)cyclohexyl acetate (1h)[3]



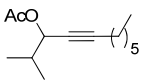
Propargyl acetate **1h** was obtained according to Method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 -7.44 (m, 2H), 7.29 -7.28 (m, 3H), 2.24 -2.19 (m, 2H), 2.07 (s, 3H), 1.93 - 1.88 (m, 2H), 1.70 -1.65 (m, 4H), 1.59 – 1.53 (m, 1H), 1.39 -1.33 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 132.4, 128.8, 128.7, 123.4, 89.8, 86.8, 76.5, 37.8, 25.8, 23.3, 22.6.

1-(Oct-1-ynyl)cyclohexyl benzoate (1i)



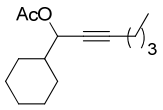
Propargyl acetate **1i** was obtained according to Method B, using 1.2 equiv. of benzoic anhydride. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17-8.15 (m, 2H), 7.69 -7.66 (m, 1H), 7.53 (t, J = 7.9 Hz, 2H), 2.20 (t, J = 6.9 Hz, 2H), 1.87-1.84 (m, 2H), 1.70-1.66 (m, 2H), 1.57 -1.24 (m, 14H), 0.88 (t, J = 6.9Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.5, 130.5, 128.9, 128.4, 84.8, 83.9, 68.8, 40.3, 31.3, 28.7, 28.5, 25.3, 23.4, 22.5, 18.6, 14.0. IR (film): $\tilde{\upsilon}$ = 2929, 2856, 1791, 1450, 1330, 1212, 1055, 996, 962, 704, 616 cm^{-1}

2-Methylundec-4-yn-3-yl acetate (5a)



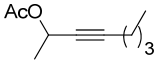
Propargyl acetate **5a** was obtained according to Method A. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.24 (dt, J = 5.6, 2.0 Hz, 1H), 2.24 (td, J = 5.6, 2.0 Hz, 2H), 2.10 (s, 3H), 2.02 (m, 1H), 1.60-1.27 (m, 8H), 1.03 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 86.8, 76.1, 69.5, 32.5, 31.3, 28.5 (2 x C), 22.5, 21.1, 18.7, 18.3, 17.5, 14.0. IR (film): $\tilde{\upsilon}$ = 2961, 2931, 2858, 1741, 1466, 1370, 1231, 1157, 1018, 980 cm^{-1}. HRMS (ESI): *m/z*: calcd for $C_{14}H_{24}O_2Na$: 247.1668. Found: 247.1668

1-Cyclohexylhept-2-ynyl acetate (5b)[3]



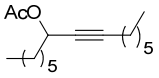
Propargyl acetate **5b** was obtained according to Method A. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.20 (d, J = 6.0 Hz, 1H), 2.21 (t, J = 7.0 Hz ,2H), 2.07 (s, 3H), 1.84 - 1.58 (m, 5H), 1.49 (quint, J = 7.2 Hz, 2H), 1.39 (Sext, J = 7.2 Hz, 2H), 1.27 – 1.03 (m, 6H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 87.3, 77.0, 69.4, 42.6, 31.2, 29.2, 28.7, 26.9, 26.4, 26.3, 22.5, 21.7, 19.0, 14.1.

Oct-3-yn-2-yl acetate (5c)[3]



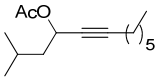
Propargyl acetate **5c** was obtained according to Method B. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.44 (qt, J = 6.8, 2.0 Hz, 1H), 2.20 (td, J = 7.0, 2.0 Hz, 2H), 2.06 (s, 3H), 1.53 - 1.34 (m, 7H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 85.6, 78.6, 60.9, 30.6, 21.9, 21.8, 21.2, 18.4, 13.6.

Pentadec-8-yn-7-yl acetate (5d)



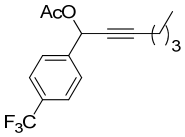
Propargyl acetate **5d** was obtained according to Method A. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.29 (tt, J = 6.9, 2.0 Hz, 1H), 2.13 (td, J = 6.9, 2.0 Hz, 2H), 2.01 (s, 3H), 1.69-1.62 (m, 2H), 1.43 (quint., J = 6.9 Hz, 2H), 1.33-1.20 (m, 14H), 0.83 (t, J = 6.9 Hz, 3H), 0.82 (t, J = 6.9 Hz, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 86.8, 78.2, 65.2, 35.6, 32.2, 31.8, 29.3, 29.0, 29.0, 25.5, 23.1 (2 x C), 21.7, 19.2, 14.6, 14.5. IR (film): $\tilde{\upsilon}$ = 2928, 2857, 1741, 1458, 1370, 1231, 1159, 1112, 1018, 963, 726, 606 cm^{-1}. HRMS (ESI): *m/z*: calcd for $C_{17}H_{30}O_2Na$: 289.2138. Found: 289.2139.

2-Methyldodec-5-yn-4-yl acetate (5e)



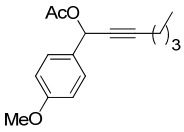
Propargyl acetate **5e** was obtained according to Method A. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (tt, J = 7.2, 2.0 Hz, 1H), 2.22 (td, J = 7.2, 2.0 Hz, 2H), 2.09 (s, 3H), 1.80 (m, 1H), 1.72-1.59 (m, 2H), 1.52 (quint., J = 6.9 Hz, 2H), 1.41-1.29 (m, 6H), 0.96 (d, J = 6.9 Hz, 6H), 0.92 (t, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 86.2, 77.8, 63.4, 44.0, 31.3, 28.4, 24.8, 22.6, 22.5, 22.3, 21.1, 18.7, 14.0. IR (film): $\tilde{\upsilon}$ = 2956, 2931, 2858, 1741, 1467, 1370, 1231, 1163, 1016, 960 cm^{-1}. HRMS (ESI): *m/z*: calcd for $C_{15}H_{26}O_2Na$: 261.1825. Found: 261.1825.

1-(4-(Trifluoromethyl)phenyl)hept-2-ynyl acetate (5f)[3]



Propargyl acetate **5f** was obtained according to Method A. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 4H), 6.40 (t, J = 2.0 Hz, 1H), 2.19 (td, J = 7.1, 2.0 Hz, 2H), 2.02 (s, 3H), 1.47-1.30 (m, 4H), 0.83 (t, J = 7.4 Hz, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 142.2, 131.4 (q, $J_{C\text{-}F}$ = 32 Hz), 128.5, 126.1 (q, $J_{C\text{-}F}$ = 4Hz), 124.5 (q, J $_{C\text{-}F}$ = 270 Hz), 89.8, 76.6, 65.9, 31.0, 22.5, 21.6, 19.1, 14.1.

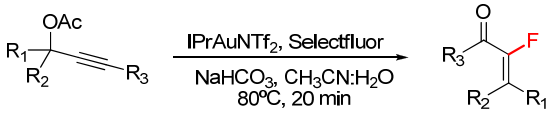
1-(4-Methoxyphenyl)hept-2-ynyl acetate (5g)[3]



Propargyl acetate **5g** was obtained according to Method A. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.42 (s, 1H), 3.81 (s, 3H), 2.27 (t, J = 7.0 Hz, 2H), 2.07 (s, 3H), 1.52 (quint, J = 7.2 Hz, 2H), 1.41 (sext, J = 7.2 Hz, 2H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 159.9, 129.9, 129.3, 113.8, 88.1, 76.8, 65.8, 55.3, 30.5, 21.9, 21.2, 18.5, 13.6.

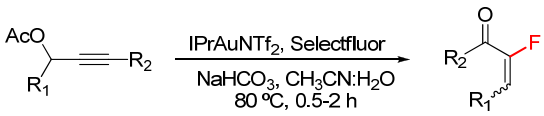
5.3 General procedures for gold catalyzed rearrangement and fluorination of propargyl acetates.

5.3.1 General procedure for tertiary acetates



The corresponding propargyl acetate (1 equiv.), followed by $IPrAuNTf_2$ (0.05 equiv.) were added to a solution of Selectfluor (2 equiv.) and $NaHCO_3$ (1 equiv.,) in $MeCN:H_2O$ (20:1, 0.02 M), The reaction was stirred for 15-30 min at 80 ^{o}C and monitored by TLC. Upon reaction completion, the mixture was diluted with DCM (5 ml) and an aqueous solution of $Na_2S_2O_3$ (5% v/v) (2 ml) was added. The mixture was extracted with DCM (3 x 5 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by silica gel flash column chromatography (Pentane/diethyl ether = 100/1) to yield the desired α-fluoroenones **2**.

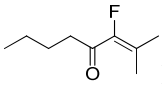
5.3.2 General procedures for secondary acetates.



The corresponding propargyl acetate (1 equiv.) followed by $IPrAuNTf_2$ (0.05 equiv.) were added to a solution of Selectfluor (2 equiv.) and $NaHCO_3$ (1 equiv.) in $MeCN:H_2O$ (20:1, 0.1 M). The reaction was stirred for 0.5-2h at 80 ^{o}C and was monitored by TLC. When the reaction was finished, the mixture was diluted with DCM (5 ml) and an aqueous solution of $Na_2S_2O_3$ (5% v/v) (2 ml) was added. The mixture was extracted with DCM (3 x 5 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified through silica gel flash column chromatography (Pentane/diethyl ether = 100/1) to yield the desired α-fluoroenones **6**.

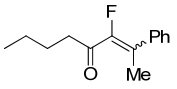
5.4 Characterization of products

3-fluoro-2-methyloct-2-en-4-one (2a)



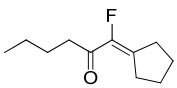
Following the general procedure, compound **2a** was isolated in 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.57 (dt, J = 7.4, 3.8 Hz, 2H), 2.08 (d, J = 3.4 Hz, 3H), 1.83 (d, J = 4.1 Hz, 3H), 1.58 (quint, J = 7.2 Hz, 2H), 1.33 (quint, J = 7.2 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.0 (d, $J_{C\text{-}F}$ = 38.2 Hz), 151.5 (d, $J_{C\text{-}F}$ = 247.4 Hz), 127.9 (d, $J_{C\text{-}F}$ = 14.9 Hz), 39.9 (d, $J_{C\text{-}F}$ = 2.4 Hz), 25.9 (d, $J_{C\text{-}F}$ = 2.4 Hz), 22.8, 19.0 (d, $J_{C\text{-}F}$ = 23.8 Hz), 18.9 (d, $J_{C\text{-}F}$ = 16.7 Hz), 14.3. IR (film): $\tilde{\upsilon}$ = 2960, 1699, 1638, 1373, 1261, 1183, 1138, 1019, 911, 808, 730 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_9H_{15}FO$: 158.1107, found: 158.1106.

3-fluoro-2-phenyloct-2-en-4-one (2b)



Following the general procedure, compound **2b** was isolated in 84% yield as an unseparable *E:Z* mixture of olefins in a ratio 1.5:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.32 (m, 8H, major and minor), 7.17-7.16 (m, 2H, major and minor), 2.68 (dt, J = 7.3, 3.9 Hz, 2H, minor), 2.43 (d, J = 3.6 Hz, 3H, minor), 2.42 (dt, J = 7.7, 3.3 Hz, 2H, major), 2.13 (d, J = 3.5 Hz, 3H, major), 1.65 (quint, J = 7.2 Hz, 2H, minor), 1.46 (quint, J = 7.2 Hz, 2H, major), 1.32 (quint, J = 7.2 Hz, 2H, minor), 1.22 (quint, J = 7.2 Hz, 2H, major), 0.94 (t, J = 7.2 Hz, 3H, minor), 0.84 (t, J = 7.2 Hz, 3H, major). ^{13} C NMR (100 MHz, $CDCl_3$): δ = 197.8 (d, $J_{C\text{-}F}$ = 38.1 Hz), 195.1 (d, $J_{C\text{-}F}$ = 34.6 Hz), 151.4 (d, $J_{C\text{-}F}$ = 256.3 Hz), 150.4 (d, $J_{C\text{-}F}$ = 253.9 Hz), 138.9 (d, $J_{C\text{-}F}$ = 5.9 Hz), 138.4 (d, $J_{C\text{-}F}$ = 1.8 Hz), 129.7 (d, $J_{C\text{-}F}$ = 18.4 Hz), 128.9, 128.7, 128.6 (d, $J_{C\text{-}F}$ = 4.2 Hz), 128.4, 128.1(d, $J_{C\text{-}F}$ = 2.9 Hz), 40.3, 26.0 (d, $J_{C\text{-}F}$ = 2.4 Hz), 25.9 (d, $J_{C\text{-}F}$ = 1.8 Hz), 22.8, 22.7, 20.0 (d, $J_{C\text{-}F}$ = 7.7 Hz), 18.4 (d, $J_{C\text{-}F}$ = 1.5 Hz), 14.3, 14.2. (Of the two sets of signals expected for the two isomers three carbon signals are missing due to overlapping). IR (film): $\tilde{\upsilon}$ = 2959, 2933, 2872, 1698, 1622, 1492, 1442, 1404, 1376, 1258, 1197, 1120, 1376, 1258, 1197, 1120, 1068, 1026, 911, 761, 732, 696 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{14}H_{17}FO$: 220.1263, found: 220.1253.

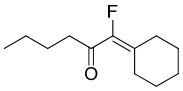
1-Cyclopentylidene-1-fluorohexan-2-one (2c)[5]



Following the general procedure, compound **2c** was isolated in 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.71-2.67 (m, 2H), 2.58 (dt, J = 7.4, 3.3 Hz, 2H), 2.50-2.46 (m, 2H), 1.74 (quint, J = 7.2 Hz, 2H), 1.67 (quint, J = 6.6 Hz, 2H), 1.58 (quint, J = 7.2 Hz, 2H), 1.35 (sext, J = 7.4 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3

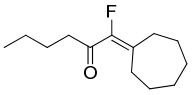
(d, $J_{C\text{-}F}$ = 35.2 Hz), 149.7 (d, $J_{C\text{-}F}$ = 249.1 Hz), 140.0 (d, $J_{C\text{-}F}$ = 14.3 Hz), 39.3 (d, $J_{C\text{-}F}$ = 2.9 Hz), 31.7 (d, $J_{C\text{-}F}$ = 1.7 Hz), 31.0 (d, $J_{C\text{-}F}$ = 3.6 Hz), 27.6, 26.0, 25.9 (d, $J_{C\text{-}F}$ = 2.3 Hz), 22.9, 14.4.

1-cyclohexylidene-1-fluorohexan-2-one (2d)



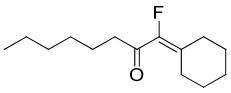
Following the general procedure, compound **2d** was isolated in 71% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.74-2.71 (m, 2H), 2.59 (dt, J = 7.6, 3.9 Hz, 2H), 2.30-2.28 (m, 2H), 1.63-1.54 (m, 8H), 1.34 (sext, J = 6.9 Hz, 2H), 0.91 (t, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.8 (d, $J_{C\text{-}F}$ = 38.7 Hz), 148.9 (d, $J_{C\text{-}F}$ = 247.3 Hz), 134.9 (d, $J_{C\text{-}F}$ = 12.5 Hz), 40.5, 28.2 (d, $J_{C\text{-}F}$ = 1.7 Hz), 27.9 (d, $J_{C\text{-}F}$ = 10.1 Hz), 27.8 (d, $J_{C\text{-}F}$ = 1.7 Hz), 27.7 (d, $J_{C\text{-}F}$ = 2.3 Hz), 26.6, 26.0 (d, $J_{C\text{-}F}$ = 2.3 Hz), 22.9, 14.4. IR (film): $\tilde{\upsilon}$ = 2933, 2858, 1698, 1633, 1450, 1405, 1351, 1256, 1179, 1117, 1048, 908, 855, 807, 732, 647 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{12}H_{19}FO$: 198.1420, found: 198.1419.

1-Cycloheptylidene-1-fluorohexan-2-one (2e)



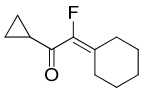
Following the general procedure, compound **2e** was isolated in 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74-2.71 (m, 2H), 2.58 (dt, J = 7.5, 4.0 Hz, 2H), 2.44-2.40 (m, 2H), 1.65-1.49 (m, 10H), 1.33 (sext, J = 6.9 Hz, 2H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.5 (d, $J_{C\text{-}F}$ = 40.7 Hz), 150.7 (d, $J_{C\text{-}F}$ = 248.7 Hz), 137.5 (d, $J_{C\text{-}F}$ = 11.3 Hz), 39.6 (d, $J_{C\text{-}F}$ = 2.2 Hz), 29.4, 29.4 (d, $J_{C\text{-}F}$ = 9.7 Hz), 29.2 (d, $J_{C\text{-}F}$ = 2.2 Hz), 29.1, 27.2 (d, $J_{C\text{-}F}$ = 2.5 Hz), 26.5 (d, $J_{C\text{-}F}$ = 1.5 Hz), 25.4 (d, $J_{C\text{-}F}$ = 2.5 Hz), 22.3, 13.9. IR (film): $\tilde{\upsilon}$ = 2928, 2857, 1696, 1620, 1455, 1261, 1168, 1104, 1041, 911, 808, 733 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{13}H_{21}FO$: 212.1577, found: 212.1577.

1-Cyclohexylidene-1-fluorooctan-2-one (2f)



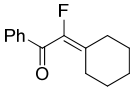
Following the general procedure, compound **2f** was isolated in 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75-2.72 (m, 2H), 2.58 (dt, J = 7.4, 3.7 Hz, 2H), 2.31-2.28 (m, 2H), 1.64-1.55 (m, 8H), 1.33-1.27 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3 (d, $J_{C\text{-}F}$ = 41.4 Hz), 148.3 (d, $J_{C\text{-}F}$ = 247.9 Hz), 134.3 (d, $J_{C\text{-}F}$ = 11.4 Hz), 40.2 (d, $J_{C\text{-}F}$ = 2.2 Hz), 31.6, 28.9, 27.6 (d, $J_{C\text{-}F}$ = 2.2 Hz), 27.3 (d, $J_{C\text{-}F}$ = 9.9 Hz), 27.2 (d, $J_{C\text{-}F}$ = 1.8 Hz), 27.1 (d, $J_{C\text{-}F}$ = 2.9 Hz), 26.0, 23.3 (d, $J_{C\text{-}F}$ = 2.2 Hz), 22.5, 14.0. IR (film): $\tilde{\upsilon}$ = 2930, 2857, 1699, 1634, 1450, 1404, 1352, 1254, 1175, 1117, 1051, 978, 773 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{14}H_{23}FO$: 226.1733, found: 226.1733.

2-Cyclohexylidene-1-cyclopropyl-2-fluoroethanone (2g)



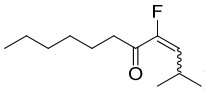
Following the general procedure, compound **2g** was isolated in 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.72-2.70 (m, 2H), 2.47-2.42 (m, 1H), 2.35-2.31 (m, 2H), 1.66-1.56 (m, 6H), 1.11-1.06 (m, 2H), 0.96-0.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.5 (d, $J_{C\text{-}F}$ = 39.6 Hz), 148.3 (d, $J_{C\text{-}F}$ = 247.2 Hz), 133.7 (d, $J_{C\text{-}F}$ = 13.2 Hz), 27.5 (d, $J_{C\text{-}F}$ = 2.2 Hz), 27.4 (d, $J_{C\text{-}F}$ = 9.5 Hz), 27.3 (d, $J_{C\text{-}F}$ = 2.6 Hz), 27.2 (d, $J_{C\text{-}F}$ = 1.8 Hz), 26.0, 17.8, 17.7. IR (film): $\tilde{\upsilon}$ = 2933, 2857, 1683, 1632, 1449, 1382, 1253, 12001177, 1050, 979, 731 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{11}H_{15}FO$: 182.1107, Found: 182.1107.

2-Cyclohexylidene-2-fluoro-1-phenylethanone (2h)[6]



Following the general procedure, compound **2h** was isolated in 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88-7.85 (m, 2H), 7.56 (tt, *J* = 6.6, 1.3 Hz, 1H), 7.47-7.43 (m, 2H), 2.50-2.48 (m, 2H), 2.49-2.41 (m, 2H), 1.72-1.60 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.7 (d, $J_{C\text{-}F}$ = 34.8 Hz), 147.9 (d, $J_{C\text{-}F}$ = 249.4 Hz), 137.1 (d, $J_{C\text{-}F}$ = 3.6 Hz), 133.7 (d, $J_{C\text{-}F}$ = 11.3 Hz), 133.0, 129.4(d, $J_{C\text{-}F}$ = 4.4 Hz), 128.3, 28.0 (d, $J_{C\text{-}F}$ = 2.9 Hz), 27.6 (d, $J_{C\text{-}F}$ = 2.6 Hz), 27.2 (d, $J_{C\text{-}F}$ = 1.4 Hz), 27.1 (d, $J_{C\text{-}F}$ = 8.8 Hz), 26.1. IR (film): $\tilde{\upsilon}$ = 2934, 2857, 1671, 1597, 1448, 1289, 1226, 1182, 1149, 1127, 960, 908, 731 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{14}H_{15}FO$: 218.1, found: 218.1.

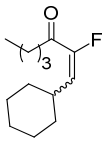
4-Fluoro-2-methylundec-3-en-5-one (6a)



Following the general procedure, compound **6a** was isolated in 71% yield as an unseparable *E:Z* mixture of olefins in a ratio 4:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (dd, $J_{H\text{-}F}$ = 35.0 Hz, *J* = 9.2 Hz, 1H, minor isomer), 5.51 (dd, $J_{H\text{-}F}$ = 23.7 Hz, *J* = 10.7 Hz, 1H, major isomer), 3.42-2.32 (m, 1H, major isomer), 2.86-2.78 (m, 1H, minor isomer), 2.61-2.56 (m, 4H, major and minor isomer), 1.62-1.56 (m, 4H, major and minor isomers), 1.33-1.25 (m, 12H, major and minor isomers), 1.07 (d, *J* = 6.8 Hz, 6H, minor isomer), 1.02 (dd, *J* = 6.7, 0.9 Hz, 6H, major isomer), 0.90-0.86 (m, 6H, minor and major isomers). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.6 (d, $J_{C\text{-}F}$ = 39.9 Hz), 195.2 (d, $J_{C\text{-}F}$ = 35.7 Hz), 154.2 (d, $J_{C\text{-}F}$ = 261.0 Hz), 152.7 (d, $J_{C\text{-}F}$ = 253.9 Hz), 128.5 (d, $J_{C\text{-}F}$ = 15.5 Hz), 125.6 (d, $J_{C\text{-}F}$ = 11.3 Hz), 40.3 (d, $J_{C\text{-}F}$ = 3.5 Hz), 38.3, 32.1, 32.0, 29.4, 29.3, 25.3 (d, $J_{C\text{-}F}$ = 5.9 Hz), 25.1 (d, $J_{C\text{-}F}$ = 2.9 Hz), 24.1, 23.5 (d, $J_{C\text{-}F}$ = 1.8 Hz), 23.2 (d, $J_{C\text{-}F}$ = 2.4 Hz), 23.0, 22.6 (d, $J_{C\text{-}F}$ = 1.2 Hz), 14.5. (Of the two sets of signals expected for the two isomers two carbon signals are missing due to overlapping).

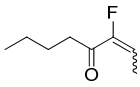
IR (film): $\tilde{\upsilon}$ = 2931, 1706, 1641, 1466, 1373, 1260, 1098, 904, 808, 725 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{12}H_{21}FO$: 200.1576, found: 200.1577.

1-Cyclohexyl-2-fluorohept-1-en-3-one (6b)



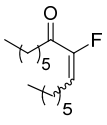
Following the general procedure, compound **6b** was obtained in 72% yield as a *E:Z* mixture of olefins in a ratio 4.5:1. Major isomer: ^{1}H NMR (400 MHz, TMSCl + $CDCl_3$): δ = 5.47 (dd, J_{H-F} = 23.2 Hz, J = 10.2 Hz, 1H), 3.02-2.99 (m, 1H), 2.54 (dt, J_{H-F} = 3.5 Hz, J = 7.3 Hz, 2H), 1.32-1.23 (m, 6H), 1.03-1.00 (m, 8H), 0.86 (t, J = 7.3 Hz, 3H) . ^{13}C NMR (100 MHz, TMSCl + $CDCl_3$): δ = 197.5 (d, J_{C-F} = 38 Hz), 153.3 (d, J_{C-F} = 250 Hz), 127.1 (d, J_{C-F} = 15.3 Hz), 40.0 (d, J_{C-F} = 2.9 Hz), 34.6 (d, J_{C-F} = 5.2 Hz), 33.3 (d, J_{C-F} = 2.2 Hz), 26.3, 25.9, 25.6, 22.8, 14.4. Minor isomer: ^{1}H NMR (400 MHz, TMSCl + $CDCl_3$): δ = 5.91 (dd, J_{H-F} = 35.3 Hz, J = 9.7 Hz, 1H), 3.02-2.99 (m, 1H), 2.54 (dt, J_{H-F} = 3.5 Hz, J = 7.3 Hz, 2H), 1.32-1.23 (m, 6H), 1.03-1.00 (m, 8H), 0.86 (t, J = 7.3 Hz, 3H) . ^{13}C NMR (100 MHz, TMSCl + $CDCl_3$): δ = 194.7 (d, J_{C-F} = 31 Hz), 153.9 (d, J_{C-F} = 259 Hz), 123.7 (d, J_{C-F} = 12.1 Hz), 37.5, 33.9 (d, J_{C-F} = 2.2 Hz), 32.1 (d, J_{C-F} = 1.8 Hz), 25.8, 25.1, 22.3, 22.2, 14.0. IR (film): $\tilde{\upsilon}$ = 2928, 2853, 1706, 1638, 1449, 1374, 1293, 1260, 1164, 1099, 1042, 803 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{13}H_{21}FO$: 212.1576. Found: 212.1574.

3-Fluorooct-2-en-4-one (6c)



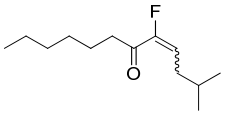
Following the general procedure, compound **6c** was isolated in 67% yield as an unseparable *E:Z* mixture of olefins in a ratio 1.2:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.11 (dq, J_{H-F} = 34.2 Hz, J = 7.4 Hz, 1H), 5.82 (dq, J_{H-F} = 22.2 Hz, J = 7.7 Hz, 1H), 2.65-2.60 (m, 4H), 2.04 (dd, J_{H-F} = 2.9 Hz, J = 7.7 Hz, 3H), 1.82 (dd, J_{H-F} = 2.9 Hz, J = 7.4 Hz, 3H), 1.67-1.58 (m, 4H), 1.42-1.33 (m, 4H), 0.97-0.93 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9 (d, J_{C-F} = 37.5 Hz), 194.7 (d, J_{C-F} = 34.5 Hz), 156.6 (d, J_{C-F} = 259.9 Hz), 154.4 (d, J_{C-F} = 252.7 Hz), 116.6 (d, J_{C-F} = 21.4 Hz), 114.5 (d, J_{C-F} = 13.1 Hz), 40.0 (d, J_{C-F} = 2.9 Hz), 38.0, 26.2 (d, J_{C-F} = 1.2 Hz), 25.6 (d, J_{C-F} = 1.6 Hz), 22.8 (d, J_{C-F} 4.1 Hz), 14.4 (d, J_{C-F} = 3.5 Hz), 11.7 (d, J_{C-F} = 6.5 Hz) 10.2 (d, J_{C-F} = 4.7 Hz). (Of the two sets of signals expected for the two isomers two carbon signals are missing due to overlapping). IR (film): $\tilde{\upsilon}$ = 2960, 2874, 1707, 1654, 1260, 1092, 1012, 913, 799, 734 cm^{-1}. HRMS (EI): *m/z*: calcd for $C_8H_{14}FO$: 145.1029 Found: 145.1027.

8-Fluoropentadec-8-en-7-one (6d)



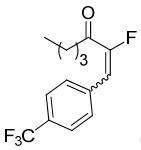
Following the general procedure, compound **6d** was obtained in a 67% yield as a *E:Z* mixture of olefins in a ratio 2:1. Major isomer: ^{1}H NMR (400 MHz, TMSCl + $CDCl_3$): δ = 5.69 (dt, $J_{H\text{-}F}$ = 23 Hz, J = 8.1 Hz, 1H), 2.59 (td, $J_{H\text{-}F}$ = 3.4 Hz, J = 7.2 Hz, 2H), 2.54-2.48 (m, 2H), 1.61-1.54 (m, 2H), 1.43-1.26 (m, 14H), 0.90-0.86 (m, 6H). ^{13}C NMR (100 MHz, TMSCl + $CDCl_3$): δ = 197.1 (d, $J_{C\text{-}F}$ = 38 Hz), 153.4 (d, $J_{C\text{-}F}$ = 253 Hz), 121.6 (d, $J_{C\text{-}F}$ = 17.6 Hz), 39.8 (d, $J_{C\text{-}F}$ = 2.9 Hz), 31.6 (d, $J_{C\text{-}F}$ = 3.2 Hz), 29.3 (d, $J_{C\text{-}F}$ = 2.0 Hz), 28.9, 28.8, 25.3, 25.2, 23.0 (d, $J_{C\text{-}F}$ = 2.0 Hz), 22.6, 22.5, 14.1, 14.0. Minor isomer: ^{1}H NMR (400 MHz, TMSCl + $CDCl_3$): δ = 6.03 (dt, $J_{H\text{-}F}$ = 35 Hz, J = 7.9 Hz, 1H), 2.61-2.57 (m, 2H), 2.26-2-20 (m, 2H), 1.61-1.54 (m, 2H), 1.43-1.26 (m, 14H), 0.90-0.86 (m, 6H). ^{13}C NMR (100 MHz, TMSCl + $CDCl_3$): δ = 194.4 (d, $J_{C\text{-}F}$ = 31 Hz), 155.3 (d, $J_{C\text{-}F}$ = 259 Hz), 119.0 (d, $J_{C\text{-}F}$ = 12.8 Hz), 37.9, 31.5, 28.9, 28.8, 28.4 (d, $J_{C\text{-}F}$ = 1.8 Hz), 24.3, 24.2, 23.6 (d, $J_{C\text{-}F}$ = 1.2 Hz), 22.5 (2 x C), 14.0 (2 x C). IR (film): $\tilde{\upsilon}$ = 2963, 2926, 2854, 1707, 1644, 1457, 1374, 1165, 1103, 912, 742 cm^{-1}. HRMS (EI): *m/z*: calcd for $C_{15}H_{27}FO$: 242.2046 Found: 242.2047

Fluoro-2-methyldodec-4-en-6-one (6e)



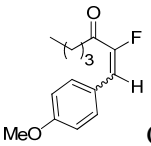
Following the general procedure, compound **6c** was isolated in 74% yield as an unseparable *E:Z* mixture of olefins in a ratio 1.6:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.01 (dt, $J_{H\text{-}F}$ = 34.2 Hz, J = 7.9 Hz, 1H, minor isomer), 5.69 (dq, $J_{H\text{-}F}$ = 23.1 Hz, J = 8.1 Hz, 1H, major isomer), 2.60-2.55 (m, 4H, major and minor isomers), 2.40 (ddd, J = 8.8, 6.9,1.8, Hz 2H, major isomer), 2.11 (ddd, J = 9.2, 6.9, 9.2 Hz, 2H, minor isomer), 1.71-1.54 (m, 6H, major and minor isomers), 1.31-1.25 (m, 12H, major and minor isomers), 0.93-0.87 (m, 18H, minor and major isomers). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.6 (d, $J_{C\text{-}F}$ = 38.7 Hz), 194.9 (d, $J_{C\text{-}F}$ = 32.2 Hz), 156.1 (d, $J_{C\text{-}F}$ = 261.6 Hz), 154.2 (d, $J_{C\text{-}F}$ = 253.9 Hz), 120.8 (d, $J_{C\text{-}F}$ = 18.5 Hz), 118.1 (d, $J_{C\text{-}F}$ = 14.3 Hz), 40.3 (d, $J_{C\text{-}F}$ = 2.9 Hz), 38.4, 34.4 (d, $J_{C\text{-}F}$ = 4.7 Hz), 33.6 (d, $J_{C\text{-}F}$ = 2.3 Hz), 32.1, 32.0, 29.3, 29.2, 29.2 (d, $J_{C\text{-}F}$ = 1.8 Hz), 28.5 (d, $J_{C\text{-}F}$ = 1.8 Hz), 24.1 (d, $J_{C\text{-}F}$ = 1.2 Hz), 23.5 (d, $J_{C\text{-}F}$ = 1.7 Hz), 23.0, 2.8, 22.7, 14.5. (Of the two sets of signals expected for the two isomers two carbon signals are missing due to overlapping). IR (film): $\tilde{\upsilon}$ = 2958, 1706, 1643, 1465, 1371, 1102, 911, 736 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{13}H_{23}FO$: 214.1733, found: 214.1734.

2-Fluoro-1-(4-(trifluoromethyl)phenyl)hept-1-en-3-one (6f)



Compound **6f** was obtained in 70% yield as an unseparable *E:Z* mixture of olefins in a ratio 2:1. ^{1}H NMR (400 MHz, TMSCl + $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.2 Hz, 2H, minor), 7.71-7-70 (m, 2H major, 2H minor), 7.63 (d, J = 8.4 Hz, 2H major), 6.85 (d, $J_{H\text{-}F}$ = 36 Hz, 1H minor), 6.68 (d, $J_{H\text{-}F}$ = 24 Hz, 1H major), 2.79 (td, $J_{H\text{-}F}$ = 2.5 Hz, J = 7.3 Hz, 2H minor), 2.72 (td, $J_{H\text{-}F}$ = 3.5 Hz, J = 7.4 Hz, 2H major), 1.73-1.59 (m, 2H major, 2H minor), 1.47-1.29 (m, 2H major, 2H minor), 0.99 (t, J = 7.4 Hz, 3H minor), 0.95 (t, J = 7.3 Hz, 3H major). ^{13}C NMR (100 MHz, TMSCl+$CDCl_3$): δ = 195.5 (d, $J_{C\text{-}F}$ = 37 Hz, major), 194.8 (d, $J_{C\text{-}F}$ = 33 Hz, minor), 154.5 (d, $J_{C\text{-}F}$ = 276 Hz, minor), 153.5 (d, $J_{C\text{-}F}$ = 262 Hz, major), 134.7, 134.6, 130.9, 130.7 (d, $J_{C\text{-}F}$ = 8.4 Hz), 130.2 (d, $J_{C\text{-}F}$ = 2.9 Hz), 125.7 (q, $J_{C\text{-}F}$ = 3.8 Hz, minor), 125.3, 125.1 (q, $J_{C\text{-}F}$ = 3.8 Hz, major), 122.6, 117.8 (d, $J_{C\text{-}F}$ = 28 Hz), 112.9 (d, $J_{C\text{-}F}$ = 5.2 Hz), 124.5 (q, J $_{C\text{-}F}$ = 270 Hz), 39.8 (d, $J_{C\text{-}F}$ = 2.4 Hz, major), 37.8 (d, $J_{C\text{-}F}$ = 1.4 Hz, minor), 25.5 (d, $J_{C\text{-}F}$ = 1.4 Hz, minor), 25.1 (d, $J_{C\text{-}F}$ = 2.0 Hz, major), 22.3 (minor), 22.2 (major), 13.8 (minor), 13.8 (major). IR (film): $\tilde{\upsilon}$ = 2962, 2926, 2854, 1709, 1641, 1322, 1166, 1125, 1068, 1018, 888, 831 cm^{-1}. HRMS (EI): *m/z*: calcd for $C_{14}H_{14}F_4O$: 274.0981. Found: 274.0971.

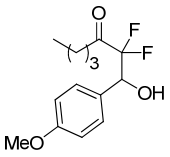
2-Fuoro-1-(4-methoxyphenyl)hept-1-en-3-one (6g)



Compound **6g** was obtained in 50% yield as an unseparable *Z:E* mixture of olefins in a ratio 2:1. Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 6.82 (d, $J_{H\text{-}F}$ = 37.3 Hz, 1H), 3.87 (s, 3H), 2.74 (td, J = 7.3, 2.2 Hz, 2H), 1.73-1.63 (m, 2H), 1.45-1.34 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.0 (d, $J_{C\text{-}F}$ = 31.6 Hz), 160.8 (d, $J_{C\text{-}F}$ = 3.4 Hz), 153.1 (d, $J_{C\text{-}F}$ = 269 Hz), 132.4 (d, $J_{C\text{-}F}$ = 8.5 Hz), 123.9 (d, $J_{C\text{-}F}$ = 4.0 Hz), 115.0 (d, $J_{C\text{-}F}$ = 5.9 Hz), 114.4, 55.3, 37.6 (d, $J_{C\text{-}F}$ = 0.8 Hz), 25.9 (d, $J_{C\text{-}F}$ = 1.4 Hz), 22.4, 13.9. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 6.64 (d, $J_{H\text{-}F}$ = 26.7 Hz, 1H), 3.86 (s, 3H), 2.69 (td, J = 7.5, 3.7 Hz, 2H), 1.73-1.63 (m, 2H), 1.45-1.34 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6 (d, $J_{C\text{-}F}$ = 30.8 Hz), 160.6 (d, $J_{C\text{-}F}$ = 1.6 Hz), 152.0 (d, $J_{C\text{-}F}$ = 253 Hz), 132.2 (d, $J_{C\text{-}F}$ = 2.8 Hz), 123.2 (d, $J_{C\text{-}F}$ = 10.4 Hz), 120.2 (d, $J_{C\text{-}F}$ = 28.8 Hz), 113.6, 55.3, 39.9 (d, $J_{C\text{-}F}$ = 2.1 Hz), 25.9 (d, $J_{C\text{-}F}$ = 2.1 Hz), 22.3, 13.9. IR

(film): $\tilde{\upsilon}$ = 2958, 2933, 2872, 1700, 1682, 1601, 1509, 1301, 1252, 1160, 1030, 888, 828, 769, 731, 598, 534 cm^{-1}. HRMS (EI): *m/z*: calcd for $C_{14}H_{17}FO_2$: 236.1213. Found: 236.1213.

2,2-Difluoro-1-hydroxy-1-(4-methoxyphenyl)heptan-3-one (7)

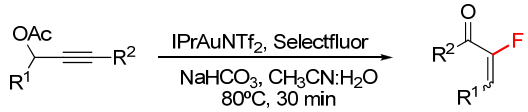


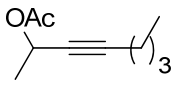
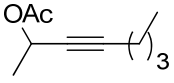
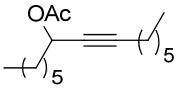
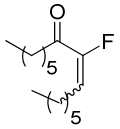
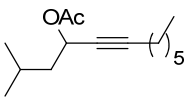
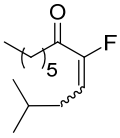
Compound **7** was obtained in 26% yield ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 5.13 (dd, $J_{H\text{-}F}$ = 16.4, 7.8 Hz, 1H), 3.85 (s, 3H), 2.64-2.58 (m, 2H), 1.62-1.54 (m, 2H), 1.32 (sext, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7 (dd, $J_{C\text{-}F}$ = 31.0, 28.0 Hz), 160.3, 129.1 (t, $J_{C\text{-}F}$ = 2.0 Hz), 126.8, 114.8 (dd, $J_{C\text{-}F}$ = 260, 254 Hz), 113.9, 72.8 (dd, $J_{C\text{-}F}$ = 29, 24 Hz), 55.3, 37.7, 24.4 21.9, 13.7; . IR (film): $\tilde{\upsilon}$ = 2960, 2934, 2873, 1737, 1612, 1513, 1464, 1401, 1249, 1175, 1069, 1030, 840, 794, 732, 580, 544 cm^{-1}; HRMS (EI):: *m/z*: calcd for $C_{14}H_{18}F_2O_3$: 272.1224. Found: 272.1225.

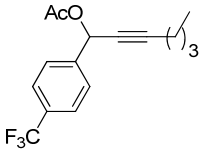
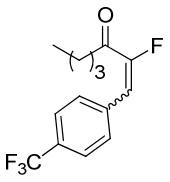
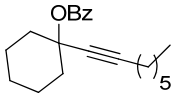
5.5 Supplementary data

5.5.1 Reaction scope (Cont. table 1)[a]

Table 3. Reaction scope (Cont. table 1)[a]



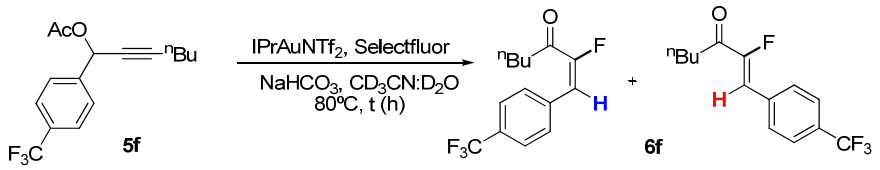
Entry	Substrate	Product	Yield (%)[b]	*E:Z* ratio
1	 **5c**	 **6c**	67[c]	1.2:1
2	 **5d**	 **6d**	67[c]	2:1
3	 **5e**	 **6e**	74[c]	1.6:1

4	 **5f**	 **6f**	70	2:1
5	 **1i**	**1i**	------	---------

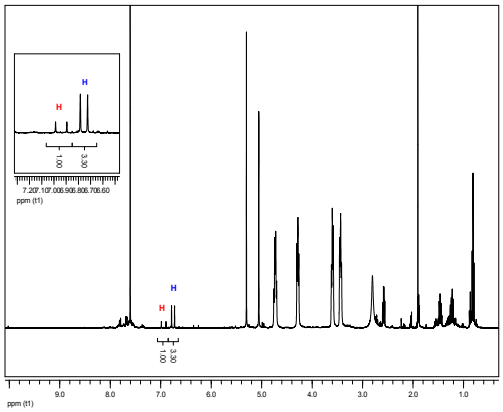
[a] Standard reaction conditions: $IPrAuNTf_2$ (5mol%), Selectfluor (2 equiv.), 20:1 CH_3CN:H_2O as solvent (substrate concentration 0.1 M), 80 ºC, 30 min. [b] Isolated yield after column chromatography.[c] Reaction time: 1-2 h.

An extensive study of secondary acetates in this tandem acyloxy migration-fluorination process was carried out (Table 3). During the migration step, a certain δ^+ is generated at the propargylic position which needs to be stabilized. Thus, in some cases, secondary acetates usually require longer times to migrate over the vicinal triple bond.[7] In fact, when acetate **5c** was submitted to the optimized reaction conditions from Table 1, a complex mixture was obtained. After some experimentation, we observed that an increase in the reaction concentration up to 0.1 M combined with longer reaction times had a beneficial effect for this type of substrates. Thus, compound **5c** was transformed into **6c** in 67% yield under the new optimized conditions (Table 3, entry 1). Substrates **5d-e** containing both linear and branched alkylic chains at the propargylic position delivered the desired fluorinated compounds **6d-e** in moderate to good yields (Table 3, entries 2-3). When aromatic substituents were placed at the propargylic position the reaction also proceeded smoothly as in the case of **5f**, which afforded ketone **6f** in 70% yield (Table 3, entry 4). In all cases, the *E* isomer was the major product detected in the reaction mixtures. Interestingly, substrate **1i**, bearing a benzoate protected alcohol, failed to deliver the corresponding α-fluoroenone (Table 3, entry 5). We reasoned that the lower ability of benzoates to undergo the [3,3]-sigmatropic rearrangement compared to acetates might account for this result.[7,8]

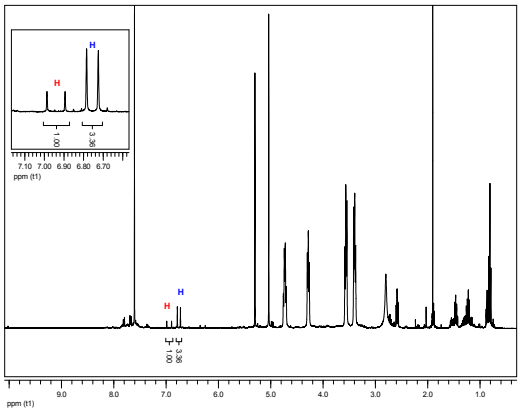
5.5.2 Isomerization experiments



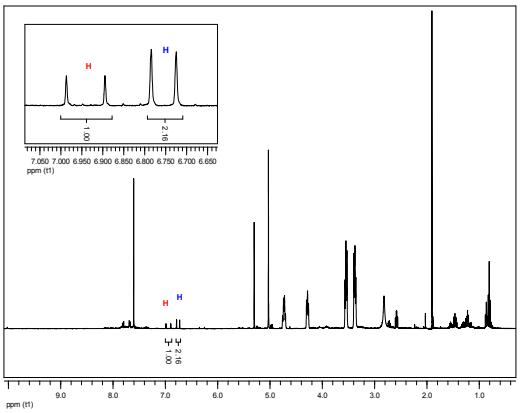
t = 0.5h

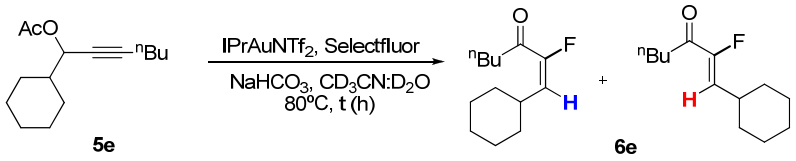


t = 1h

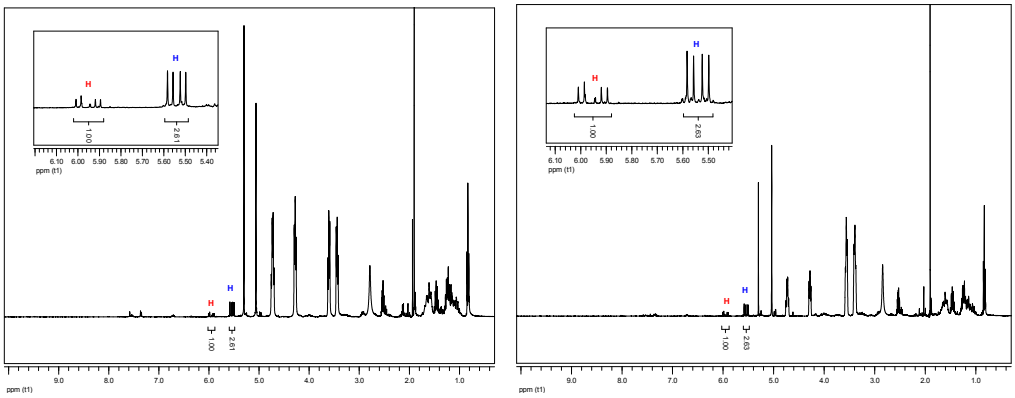


t = 3h





t = 0.5 h t = 3 h



5.6 References

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[7] Huang, X.; de Haro, T.; Nevado, C. *Chem. Eur. J.* **2009**, *15*, 5904.

[8] de Haro, T.; Gómez-Bengoa, E.; Cribiu, R.; Huang, X.; Nevado, C. *Manuscript in preparation*

CHAPTER 6

Gold Catalyzed Synthesis of α-Fluoroacetals and α-Fluoro-ketones from Alkynes

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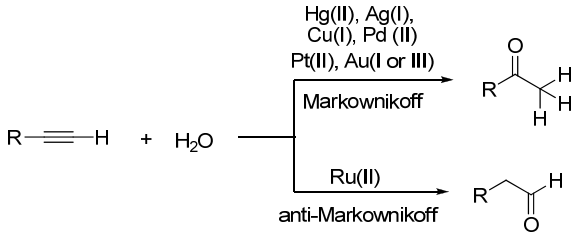
Teresa de Haro and Cristina Nevado*

(*Adv. Synth. Catal.* **2010**, *352*, 2767)

Metal complexes of alkynes are important intermediates in many transformations such as 1,n-enyne cyclization, polymerization and metathesis reactions.[1] According to the classical Dewar-Chatt-Duncanson model,[2] the bonding between the metal and the alkyne can be described as a combination of a σ- and a π-interaction (by overlap of the π-system of the acetylene with dsp orbitals of the metal and from filled d-orbitals of the metal into π*-orbital of acetylene respectively). Late transition metals such as Hg, Cu, Pd, Pt, Au, etc... show a more important σ- contribution to the bond with almost no back-donation, thus diminishing the electron density on the alkyne and increasing its susceptibility to a nucleophilic attack.[3] Such reactivity mode has been thoroughly exploited over the past century. Alkynes, as abundant hydrocarbon source, have been reported to undergo the addition of C, N, S and O nucleophiles upon π-activation with transition metals.[4] The nucleophilic addition of water or alcohols to alkynes has attracted enormous attention since it represents an excellent way to obtain aldehydes, ketones or their corresponding acetals depending on whether the reaction occurs in a Markownikoff or anti- Markownikoff manner (Scheme 1).[5] Hg(II) was the first metal used to promote the hydration of alkynes in an industrially relevant process for the synthesis of acetaldehyde and crotonaldehyde.[6,7] Soon it became clear that mercury had to be replaced, not only because of its toxicity but also due to its rapid reduction to catalytically inactive Hg(0) species under the reaction conditions. Other metals such as Ag(I), Cu(I), Tl(III), Pd(II), Ru(III), Rh(III) and Os(II) were explored, although the reactions proved to be more limited in scope.[8] In contrast, Pt(II),[9] Au(I) and Au(III)[10] have showed a much better profile in terms of scope, selectivity and catalytic activity. Noticeably, the most active catalysts reported so far are those based on gold,[10c-d,11] which due to the strong relativistic effects governing its coordination behaviour, is able to activate unsaturated moieties in an unparallel mild and efficient manner.

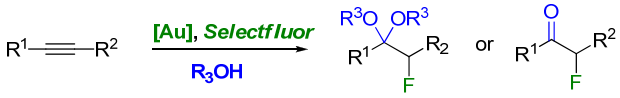
Scheme 1. Metal-catalyzed hydration of alkynes



Our ongoing program is focused in the development of novel methodologies for the construction of molecular complexity triggered by the π-activation ability of gold species.[12] We have recently developed an efficient method to synthesize *α*-fluoroenones based on a tandem gold-catalyzed process starting from easily available propargyl acetates.[13] The efficient formation of C-F bonds represents a major interest in organic chemistry due to the rather unique properties of fluorinated compounds compared to their corresponding C-H counterparts: hydrophobicity, solubility, metabolic stability, etc...[14] Gold-complexes have only now started to arise as a potential source of catalytic fluorinations, as shown independently by the groups of Sadighi and Governeur.[15]

Here we report a novel and highly efficient method to selectively synthesize α-fluoroacetals or α-fluoro-ketones from alkynes using $Ph_3PAuNTf_2$ as catalyst and Selecfluor through an alkoxylation/hydration-fluorination protocol using alcohols as solvent (Scheme 2).

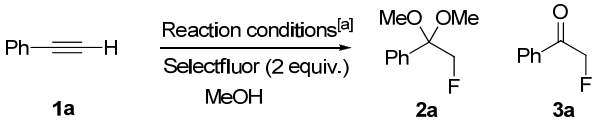
Scheme 2. Hydrofluorination of alkynes



α-Fluoroketones are important building blocks in organic chemistry and are considered compounds of intrinsic biological interest.[16] The synthesis is usually derived from the corresponding ketones, which are activated via metal enolate anion, enol ether, enamine or imines prior to electrophilic fluorination.[17] Few direct fluorinations of ketones have been reported mainly using NFTh Accufluor.[18] The use of Selectfluor as stoichiometric fluorinating agent of ketones has been reported although the substrate scope is limited and low selectivities are observed.[19] To the best of our knowledge, the selective formation of α-fluoroacetals or, alternatively, α-fluoroketones from alkynes presented here is rather unexplored.[20]

In our screening, phenylacetylene (**1a**) was used as a benchmark substrate. The results on the optimization of the reaction conditions have been summarized in Table 1.

Table 1. Optimization of the reaction conditions



1a **2a** **3a**

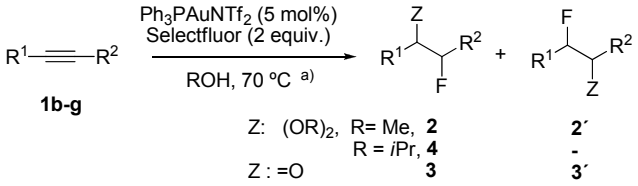
Entry	Catalyst (5 mol %)	Modifications [a]	Yield[b] (%) (**2a**)	Yield[c] (%) (**3a**)
1	Ph_3AuCl	24 h	-	-
2	Ph_3AuNTf_2	-	78	8
3	Ph_3AuNTf_2	17 h	-	Quant. [d]
4	Ph_3AuNTf_2	MeOH (anhydr.)	82	6
5	Ph_3AuNTf_2	25 ºC, 24 h	55 [e]	-
6	Ph_3AuNTf_2	0.1 M	78	8
7	Ph_3AuNTf_2	$NaHCO_3$ (1 equiv.)	-[f]	-[f]

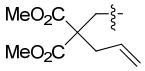
[a] Unless otherwise stated the reactions were run at 70 ºC for 2 h (0.02 M) and quenched with one drop of Et_3N before evaporation of the solvent. [b] Isolated yield after column chromatography in SiO_2 neutralized with Et_3N (2%). [c] Isolated yield after column chromatography in SiO_2. [d] Reaction was directly rotavaped. [e] Acetophenone was formed in the reaction. [f] Homocoupling of **1a** was obtained (Ref. 22).

The reaction of **1a** in the presence of commercially available Ph_3PAuCl (5 mol%) and Selecfluor (2 equiv.) in refluxing MeOH for 24 hours afforded only starting material (Table 1, entry 1). When a cationic complex such as $Ph_3PAuNTf_2$ was used, fluoro-dimethylacetal **2a** could be isolated in 78% yield after only 2 hours together with 8% of α-fluoroketone **3a** (Table 1, entry 2). **3a** was the only product obtained when the reaction was run overnight (Table 1, entry 3).[21] The reaction in the presence of anhydrous methanol slightly improved the yield in **2a**, although **3a** could still be detected in the reaction mixture (Table 1, entry 4).[22] The reaction was also performed at room temperature for 24 hours. In this case, a lower yield for **2a** was obtained due to the competitive formation of acetophenone (Table 1, entry 5). The concentration seemed not to have a pronounced effect in the reaction outcome, as reflected by entry 6. Finally, in an attempt to reduce the acidity of the media, the reaction was performed in the presence of 1 equivalent of $NaHCO_3$. Under these conditions, in contrast to the previous examples, homocoupling of **1a** was observed (Table 2, entry 7).[23] Noticeably, **2a** and **3a** were always obtained as single regioisomers, with the addition taking place at the more substituted carbon atom of the triple bond (Markownikoff).

For the sake of simplicity, we decided to use the conditions from Table 1, entry 6, to explore the reaction scope with other alkynes and alcohols (Table 2).

Table 2. Reaction scope



Entry		[a]	R^1	R^2	Products, Ratio, (Yields)[b]
1	**1b**	A	*p*-OMeC$_6$H$_4$	H	**2b**, (71)[c]
2	**1b**	B	„	H	**3b**, (93)
3	**1c**	A	*n*-C$_6$H$_{13}$	H	**2c/2c-1**,[24] 1:2, (78)
4	**1d**	A	Ph	Ph	**2d**, (92)
5	**1d**	B	„	„	**3d**, (80)[25]
6	**1d**	C	„	„	**4d**, (84)[c]
7	**1e**	A	*p*-Et-C$_6$H$_4$	*p*-Et-C$_6$H$_4$	**2e**, (73)[c]
8	**1e**	B	„	„	**3e**, (68)
9	**1f**	A	*p*-Br-C$_6$H$_4$	*p*-Br-C$_6$H$_4$	**2f**, (85)[d]
10	**1g**	A	Ph	*n*-C$_6$H$_{13}$	**2g/2g´**, 10:1,(72)
11	**1g**	B	Ph	*n*-C$_6$H$_{13}$	**3g/3g´**, 10:1,(80)
12	**1h**	A		Ph	**2h**, (86)
13	**1h**	D	„	„	**3h**, (99)

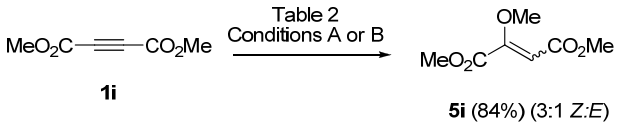
[a] Conditions A: as entry 6 in Table 1. Conditions B: as conditions A but reaction was stirred for 17 h before solvent evaporation. Conditions C: as conditions A, but with *i*-PrOH as solvent. Conditions D: as conditions A, but the crude mixture was treated with a THF/H_2O/TFA mixture (3:1:3) for 1 h. [b] Isolated yield. [c] Ketones **3b**, **3d** and **3e** could be isolated from the reaction mixtures in 5, 8 and 7% yield respectively. [d] 10% catalyst.

p-Methoxyphenyl substituted alkyne **1b** reacted efficiently to give α-fluoroacetal **2b** in 71% yield (Table 2, entry 1), whereas the corresponding ketone **3b** could be obtained in 93% yield upon prolonged reaction times (Table 2, entry 2). As previously observed for **1a**, the reaction is completely regioselective. However, a terminal alkyne with an alkyl substituent (**1c**) afforded a 1:2 mixture of regioisomeric acetals **2c** and **2c-1**[24] in 78% yield (Table 2, entry 3). Internal alkynes were also suitable substrates for this transformation. First, symmetric substrates with aromatic substituents such as **1d**, **1e** and **1f** were tested affording the corresponding acetals **2d**, **2e** and **2f** in good to excellent yields (Table 2, entries 4, 7, 9). Substrates **1d** and **1e** could also be cleanly transformed into their corresponding ketones (**3d** and **3e**) upon the appropiate conditions (Table 2, entries 5 and 8).[25] Other alcohols such as isopropanol, could be employed as solvent affording diisopropyl acetal **4d** in excellent yield from **1d** (Table 2, entry 6). In contrast, phenol or ethylene glycol afforded only unreacted

starting material. Asymmetrically disubstituted alkynes were also successfully transformed in a highly regioselective manner. Thus, **1g** was transformed into a regioisomeric mixture of acetals (**2g** and **2g´**) or ketones (**3g** and **3g´**) in a 10:1 ratio in favour of the attack at the Cα- to the aromatic ring (Table 2, entries 10-11).

1,6-Enyne **1h** was also subjected to the standard reaction conditions. In this case, the double bond is a mere spectator and only the triple bond reacts to give acetal **2h**, thus highlighting the regio- and chemoselectivity of the reaction driven by the gold coordination to the alkyne moiety (Table 2, entry 12). To obtain ketone **3h**, a one-step procedure was devised using a mixture of THF/H_2O/TFA to hydrolyse the acetal (Table 2, entry 13). Finally, dimethylacetylenedicarboxylate (**1i**) was exposed to the reaction conditions A and B from Table 2. In contrast to all previous results, the reaction afforded enol **5i** in 84% yield as a 3:1 *Z:E* mixture of isomers (Scheme 3).[26]

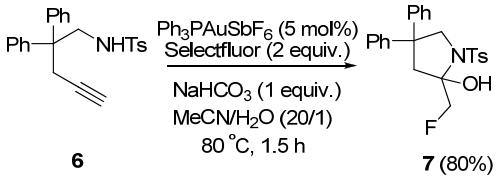
Scheme 3. Reaction of **1i**.



1i **5i** (84%) (3:1 *Z:E*)

We also decided to explore the reactivity of *N*-containing nucleophiles.[27] Thus, amide **6** was reacted in the presence of $Ph_3PAuSbF_6$ as catalyst in a mixture of acetonitrile/water. This transformation afforded aminoalcohol **7** as a single reaction product in 80% yield (Scheme 4). In the absence of gold, only starting material **6** was recovered.

Scheme 4. Amino-hydroxy fluorination of alkynes

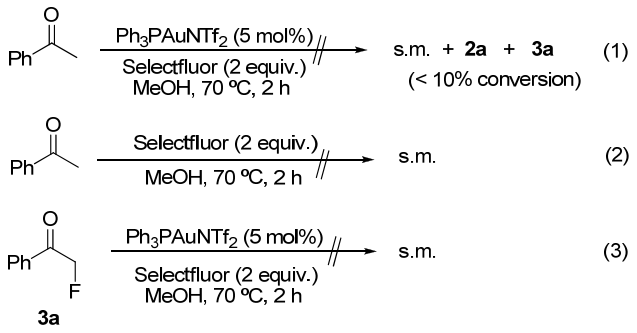


6 **7** (80%)

To gain some insight in the reaction mechanism, several experiments were designed. First, we evaluated whether the formation of α-fluorodimethylacetals (**2**) proceeded via acetalization/fluorination of the corresponding methyl ketones generated *in situ* through a standard gold catalyzed hydration of the alkyne.[10] To this end, acetophenone was subjected to the standard reaction conditions. After 2 hours, the reaction showed starting material, and only trace amounts of **2a** and **3a** could be detected by ^{1}H NMR, ruling out this mechanistic hypothesis (Scheme 5, eq. 1). In the absence of gold, the reaction afforded only starting material (Scheme 5, eq. 2).[19] α-Fluoroketone **3a** was also screened, but the corresponding

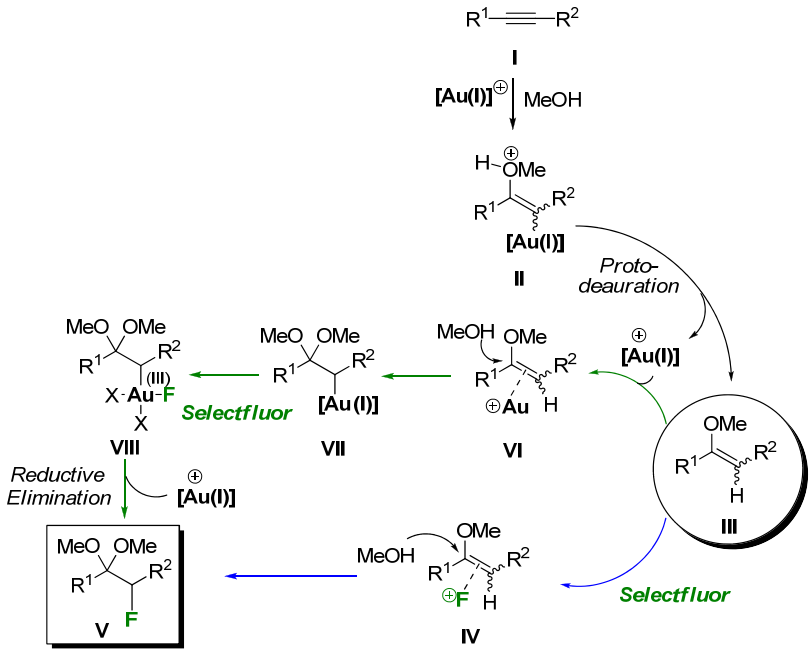
dimethylacetal **2a** could not be detected in the reaction mixture (Scheme 5, eq. 3). These results confirm the hypothesis that ketones (fluorinated or not) are not the productive intermediates for the synthesis of the corresponding acetals in these transformations.

Scheme 5. Mechanistic probes.



A different mechanistic scenario was then devised as shown in Scheme 6.

Scheme 6. Mechanistic proposal.

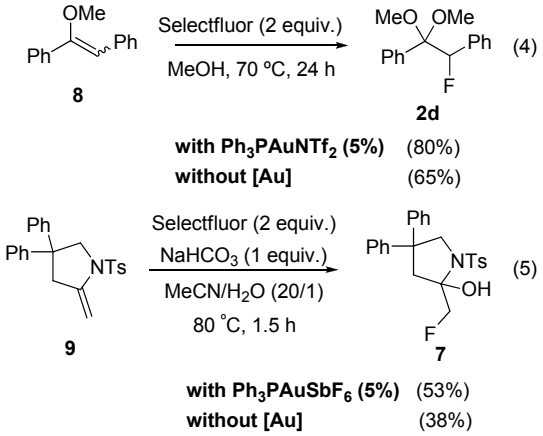


First, upon gold activation of the alkyne (**I**) a first molecule of alcohol attacks the triple bond forming an enol ether intermediate (**III**) upon protonolysis of the Csp^2-Au bond in **II**.[10b-c] The involvement of enol ethers in gold-catalyzed alkoxylation/hydration of alkynes has ample precedent.[10c,11,26] Selectfluor could then activate the *in situ* produced enol ether (**III**) to form the Csp^3-F bond with concomitant attack of a second molecule of methanol (**IV**) to give α-fluorodimethylacetals (**V**). Upon hydrolysis of the acetals in the slightly acidic media of the reaction the corresponding ketones would be obtained (Scheme 6, blue path).[28]

To test this hypothesis, enol ether **8** was prepared as previously reported by Nolan and co-workers using $IPrAuSbF_6$ (2 mol%) as catalyst.[11] When **8** was reacted in the presence of $Ph_3PAuNTf_2$ (5 mol%), and two equivalents of Selectfluor in MeOH at 70 ºC, **2d** was cleanly obtained. In the absence of gold, **2d** was also obtained although in lower yield (Scheme 7, eq. 4).[29,30] In addition, the reaction of enamine **9** under the reaction conditions of Scheme 4 afforded alcohol **7** in 53% yield in the presence of gold, whereas in the absence of the metal, **7** could only be isolated in 38% yield (Scheme 7, eq. 5).[31]

These results seem to indicate that the reaction mechanism do not exclusively proceed via the Selectfluor-mediated fluorination of a reactive enol ether/enamine intermediate. In our view, enol ether **III** could be re-activated in the presence of gold to give intermediate **VI** (as recently proposed by Corma and co- workers[26]), which could be oxidized in the presence of Selectfluor with concomitant addition of a second molecule of alcohol to give Au(III)-species (**VIII**),[32] so that the formation of the Csp^3-F bond occurs, at least partially, via reductive elimination at the gold center (Scheme 6, green path).[33]

Scheme 7. Further mechanistic probes.



In summary, we report here a gold-catalyzed synthesis of α-fluoroacetals and α-fluoroketones from alkynes using Selectfluor as the stoichiometric source of fluorine. The reaction has been applied to both terminal and internal alkynes showing a high degree of chemo- and regioselectivity. The reaction conditions allow the selective formation of acetals or ketones, highlighting the synthetic flexibility of this method. Mechanistic studies indicate that two possible reaction pathways might coexist in the reaction, since at least partially, the formation of the Csp^3-F bond in the final products occurs at the metal center.

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[21] The catalytic amount of triflimide (NTf_2H) formed in situ can hydrolyze the initially formed dimethyl acetal (**2a**) yielding the corresponding ketone (**3a**), see: Trepka, R. D.; Belisle, J. W.; Harrington, J. K. *J. Org. Chem.* **1974**, *39*, 1094.

[22] The presence of adventitious water in the reaction could also explain the formation of ketone **3a** in small amount. Nevertheless, since when the reaction was run in anhydrous methanol, still **3a** was detected, we favour the hypothesis of the brønsted acidity of triflimide to justify the hydrolysis of the acetals to the corresponding ketones.

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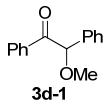
[24] For the formation of **2c-1**, see mechanistic discussion later on and ref. 28.

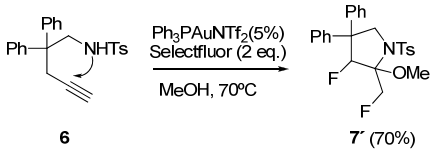
[25] 2-Methoxy-1,2-diphenylethanone (**3d-1**) was also isolated in the reaction in 8% yield.



3d-1

[26] Corma, A.; Ruiz, V. R.; Leyva-Pérez, A.; Sabater, M. J. *Adv. Synth. Catal.* **2010**, *352*, 1701.

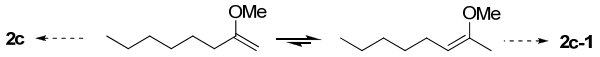
[27] The reaction of **6** under the standard conditions (Table 1, entry 6) afforded bisfluorinated compound **7´**as a 2:1 mixture of diasteroisomers. See Supporting Information for further details.



[28] The reaction of **2a** under the reaction conditions shown in entry 6 of Table 1, afforded **3a** quantitatively.

[29] In contrast, the reaction of **1i** shown in Scheme 3 stopped at enol ether **5i** likely due to the electron-withdrawing nature of the ester functions, even after prolonged reaction times.

[30] For substrate **1c**, the formation of regioisomeric fluorinated product **2c-1** can be explained by the formation of a more thermodynamically favoured trisubstituted enol ether along the reaction pathway, which seems to indicate that the fluorination reaction is slower for terminal alkynes with alkylic substituents than for those with aromatic ones (**1a-b**).



[31] Neither **8** nor **9** could be detected in the reaction mixtures of **1d** and **6** to give **2d** and **7**, respectively.

[32] (a) Wegner, H. A.; Ahles, S.; Neuenburg, M. *Chem. Eur. J.* **2008**, *14*, 11310; (b) Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 3112; (c) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.,* **2010**, *132*, 1474; (d) Iglesias, A.; Muñiz, K. *Chem. Eur. J.* **2009**, *48*, 10563; (e) de Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512.

[33] An intermediate similar to **VIII** has been already proposed to undergo gold displacement in the presence of a suitable nucleophile (ref. 32d). MeOH could displace the Au(III) in our reaction, thus explaining the formation of compound **3d-1** (ref. 25). A control experiment was performed to confirm that **3d-1** was not obtained from **3d** upon prolonged stirring under the standard reaction conditions.

Chapter 6

Experimental Section

Table of Contents

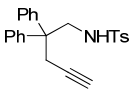
6.1 General information

NMR spectra were recorded on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual ^{1}H and ^{13}C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution electrospray ionization and electronic impact mass spectrometry was performed on a Finnigan MAT 900 (Thermo Finnigan, San Jose, CA; USA) doublefocusing magnetic sector mass spectrometer. Ten spectra were acquired. A mass accuracy ≤ 2 ppm was obtained in the peak matching acquisition mode by using a solution containing 2 <l PEG200, 2 <l PPG450, and 1.5 mg NaOAc (all obtained from Sigma-Aldrich, CH-Buchs) dissolved in 100mL MeOH (HPLC Supra grade, Scharlau, E-Barcelona) as internal standard. GC-MS analysis was done on a Finnigan Voyager GC8000 Top.

Materials and Methods: Unless otherwise stated, starting materials were purchased from Aldrich, Fluka or ABCR. All reagents were used as received. PPh_3AuCl, was prepared according to previously reported procedures.[1] PPh_3AuNTf_2 and PPh_3AuSbF_6 were formed by mixing PPh_3AuCl with the corresponding silver salt in dichloroethane upon filtration through a short pad of Celite. Except for methanol, solvents were purchased in HPLC quality, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Anhydrous methanol was obtained upon reflux over Mg and subsequent distillation under inert atmosphere. Conversion was monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F_{254}. Flash column chromatography was performed over silica gel (230-400 mesh).

6.2 Preparation and characterization of starting materials

***N*-(2,2-Diphenylpent-4-ynyl)-4-methylbenzenesulfonamide (6)**[2]

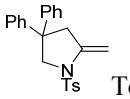


To a suspension of LDA (56.9 mmol, 1.1 equiv.) in THF at - 78 °C was added the diphenylacetonitrile (10 g, 51.8 mmol, 1 equiv.). The reaction was stirred for 30 min and warmed to room temperature. Propargyl bromide (5.5 mL, 62.2 mmol, 1.2 equiv.) was added via syringe and the reaction mixture was stirred overnight. The reaction was cooled in an ice-water bath and quenched with H_2O (100 mL), extracted with diethylether (3 x 100 mL), dried over $MgSO_4$ and solvent was removed under reduced pressure to give the crude nitrile as light yellow oil. The latter was characterized solely by ^{1}H NMR spectroscopy and used without further purification. To a suspension of $LiAlH_4$ (4.0 g, 103.6 mmol, 2.0 equiv.) in diethyl ether (70 mL) under nitrogen was added the crude nitrile (12 g, 51.8 mmol, 1 equiv.) as a

solution in diethyl ether (20 mL) dropwise. The mixture was stirred for 30 min at room temperature, then refluxed for 3 h and finally cooled to 25ºC and stirred overnight. The reaction was quenched by slow addition to a 95:5 mixture of THF:H_2O at -20 ^oC (ice-acetone bath). The solid was filtered, and washed with several portions of diethyl ether (3 x 50 mL). The combined filtrates were washed with H_2O, dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography using Hexane : EtOAc (3:1), afforded the corresponding aminoalkyne (3.0 g, 12.9 mmol) in 25 % yield.

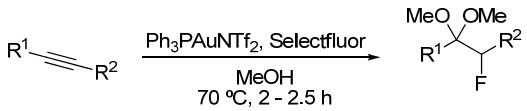
The aminoalkyne (3.0 g, 12.9 mmol, 1 equiv.) was dissolved in dichloromethane (26 mL, 0.5 M) and the solution was treated with p-toluenesulfonyl chloride (2.68 g, 14.2 mmol, 1.1 equiv.) and pyridine (3.1 mL, 38.7 mmol, 3 equiv.). The mixture was stirred at room temperature for 24 h, diluted with H_2O (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers where washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Flash chromatography of the resulting crude oil on silica gel using Hexane:AcOEt 6:1 afforded the sulfonamide **6** (3.6 g, 9.2 mmol) in 72 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.9 Hz, 2H), 7.28-7.24 (m, 8H), 7.10-7.08 (m, 4H), 3.98 (t, *J* = 6.7 Hz, 1H), 3.71 (d, *J* = 6.7 Hz, 2H), 3.05 (d, *J* = 2.7 Hz, 2H), 2.42 (s, 3H), 1.94 (t, *J* = 2.4 Hz, 1H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 143.9, 136.9, 130.2, 128.9, 128.2, 127.7, 127.6, 80.7, 72.7, 50.6, 50.0, 28.8, 22.1 IR (film): $\tilde{\upsilon}$ = 3288, 3057, 2922, 1597, 1495, 1445, 1410, 1328, 1160, 1092, 985, 814, 698, 663, 458 cm^{-1}. HRMS (ESI): *m/z*: calcd for $C_{24}H_{23}NO_2SNa$: 412.1341 found: 412.1342.

2-methylene-4,4-diphenyl-1-tosylpyrrolidine (9)[3]



To a solution of **6** (49 mg, 0.125 mmol, 1 equiv.) in THF (1.6 mL, 0.08 M), were added K_2CO_3 (87 mg, 0.625 mmol, 5 equiv.) and $Pd_2(dba)_3$ (11.4 mg, 0.0125 mmol, 0.1 equiv.). The solution was refluxed and monitored by TLC. Upon completion, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with diethyl ether (3 x 5 mL). the combined organic layers were dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (95 % Hexane/AcOEt, 1 % Et_3N) to afford the corresponding pyrrolidine **9** (0.037 mmol, 14.5 mg) in 30 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.0 Hz, 2H), 7.25-7.14 (m, 12H), 5.07 (d, *J* = 1.3 Hz, 1H), 4.36 (d, *J* = 1.3 Hz, 1H), 4.27 (s, 2H), 3.05 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 143.9, 143.0, 134.4, 129.4, 128.5, 127.2, 126.7, 126.6, 90.7, 61.0, 49.8, 45.1, 21.5. IR (film): $\tilde{\upsilon}$ = 3405, 3057, 2921, 1612, 1494, 1447, 1398, 1341, 1264, 1165, 1130, 1083, 974, 930, 734, 700, 663 cm^{-1}. HRMS (ESI): *m/z*: calcd for $C_{24}H_{23}NO_2SNa$: 412.1341 found: 412.1343.

6.3 General procedures for gold catalyzed alkoxylation/ fluorination reaction of alkynes



Condition A: $Ph_3PAuNTf_2$ (0.05 equiv.) was added to a solution of the corresponding alkyne (1 equiv.) and Selectfluor (2 equiv.) in MeOH (0.1 M). The reaction was stirred for 2 h at 70 ^oC and monitored by TLC. Upon consumption of the starting material, 1 drop of triethylamine was added and the mixture was filtered over a short path of Celite. The solvent was evaporated under reduced pressure and the residue was purified by silica gel flash column chromatography (Pentane/Diethyl ether + 2%Et_3N) to yield α-fluoroacetals **2**.

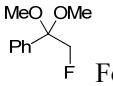
Condition B*:* As *conditions A* but reaction was stirred for 17 h and then solvent was directly evaporated under reduced pressure. The residue was purified by Silica gel flash column chromatography (Pentane/Diethyl ether) to afford α-fluoroketones **3**.

Condition C: As *conditions A* but with *i*-PrOH as solvent.

Condition D: As *conditions A* but the crude mixture was treated with a THF/H_2O/TFA mixture (3:1:3) for 1 h. The organic solvents were evaporated under reduced pressure and the residue was extracted with dichloromethane (2 x 2 mL). The organic layer was washed with brine, dried over $MgSO_4$ and rotavaped under reduced pressure to give ketones in pure form.

6.4 Characterization of products

1-(2-Fluoro-1,1-dimethoxyethyl)-benzene (2a)[4]



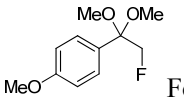
Following the general procedure A, compound **2a** was isolated in 78 % yield; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.54-7.52 (m, 2H), 7.40-7.26 (m, 3H), 4.50 (d, $J_{H\text{-}F}$ = 47.1 Hz, 2H), 3.29 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.4, 128.7, 128.5, 127.5, 100.7 (d, $J_{C\text{-}F}$ = 19.1 Hz), 83.5 (d, $J_{C\text{-}F}$ = 178.8 Hz), 49.5 (2C). IR (film): $\tilde{\upsilon}$ = 2364, 2341, 2162, 2034, 1069, 1038, 700, 669, 661, 522 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{10}H_{13}FO_2Na$: 207.0791, found: 207.0789.

2-Fluoro-1-phenylethanone (3a)[5]

Following the general procedure B, compound **3a** was isolated in 100 % yield; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90-7.88 (m, 2H), 7.64-7.61 (m, 1H), 7.51-7.48 (m, 2H), 5.5

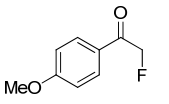
(d, $J_{H\text{-}F}$ = 47.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.5 (d, $J_{C\text{-}F}$ = 14.7 Hz), 134.4, 134.0, 129.2, 128.1 (d, $J_{C\text{-}F}$ = 2.9 Hz), 83.8 (d, $J_{C\text{-}F}$ = 202.1 Hz).

1-(2-Fluoro-1,1-dimethoxyethyl)-3-methoxybenzene (2b)[4]



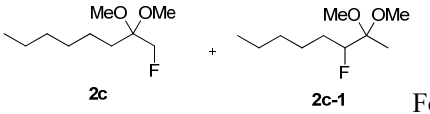
Following the general procedure A, compound **2b** was isolated in 71 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44-7.22 (m, 2H), 6.90 (d, J = 9.1 Hz, 2H), 4.47 (d, $J_{H\text{-}F}$ = 47.2 Hz, 2H), 3.80 (s, 3H), 3.26 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 130.4, 128.8, 113.8, 100.6 (d, $J_{C\text{-}F}$ = 19.8 Hz), 83.8 (d, $J_{C\text{-}F}$ = 179.7 Hz), 55.5, 49.4, 49.3. IR (film): $\tilde{\upsilon}$ = 2959, 2908, 2836, 1612, 1511, 163, 1442, 1297, 1264, 1249, 1173, 908, 835, 731 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{11}H_{15}FO_3Na$: 237.0897, found: 237.0896.

2-Fluoro-1-(4-methoxyphenyl)ethanone (3b)[6]



Following the general procedure B, compound **3b** was isolated in 93 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 9.1 Hz, 2H), 6.96 (d, J = 9.1 Hz, 2H), 5.47 (d, $J_{H\text{-}F}$ = 47.3 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2 (d, $J_{C\text{-}F}$ = 14.7 Hz), 164.5, 130.6 (d, $J_{C\text{-}F}$ = 2.9 Hz), 127.1, 114.4, 83.8 (d, $J_{C\text{-}F}$ = 182.6 Hz), 55.8.

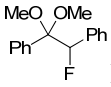
1-Fluoro-2,2-dimethoxyoctane (2c) and 3-Fluoro-2,2-dimethoxyoctane (2c-1)



Following the general procedure A, compounds **2c** and **2c-1** were obtained as a mixture 1:2 respectively in 78 % yield; Characterization of the mixture: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.52-4.35 (m, 1H$_{major}$), 4.33 (d, $J_{H\text{-}F}$ = 47.9 Hz, 2H$_{minor}$), 3.25 (s, 3H$_{major}$), 3.23 (s, 6H$_{minor}$), 3.21 (s, 3H$_{major}$), 1.69-1.52 (m, 8H$_{major\ and\ minor}$), 1.42-1.28 (m, 10H$_{major\ and\ minor}$), 1.26 (d, J = 1.5 Hz, 3H$_{major}$), 0.91-0.87 (m, 6H$_{major\ and\ minor}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.1 (d, $J_{C\text{-}F}$ = 22.7 Hz), 92.9 (d, $J_{C\text{-}F}$ = 175.7 Hz), 79.2 (d, $J_{C\text{-}F}$ = 173.2 Hz), 79.1, 77.6, 48.6 (d, $J_{C\text{-}F}$ = 1.5 Hz), 48.5, 48.3, 32.1, 32.0, 31.9, 30.5 (d, $J_{C\text{-}F}$ = 20.5 Hz), 29.7, 25.9 (d, $J_{C\text{-}F}$ = 1.8 Hz), 23.6, 22.9, 22.8, 17.0, 14.4, 14.3. Characterization of the major compound **2c-1.** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.52-4.35 (m, 1H), 3.25 (s, 3H), 3.21 (s, 3H), 1.63-1.51 (m, 3H), 1.40-1.28 (m, 5H), 1.26 (d, J = 1.50 Hz, 3H), 0.91-0.87 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.1 (d, $J_{C\text{-}F}$ = 22.7 Hz), 92.9 (d, $J_{C\text{-}F}$ = 175.7 Hz), 48.6 (d, $J_{C\text{-}F}$ = 1.5 Hz), 48.5, 31.9, 30.5 (d, $J_{C\text{-}F}$ = 20.5 Hz), 25.9 (d, $J_{C\text{-}F}$ = 1.8 Hz), 22.8, 17.0, 14.3. IR (film): $\tilde{\upsilon}$ = 2956, 2931, 2860, 2832, 1458, 1434, 1380, 1273, 1234, 1179, 1153,

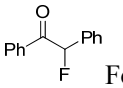
1131, 1100, 1080, 1048, 939, 908, 873 cm^{-1}; MS (ESI): *m/z*: calcd for $C_{10}H_{21}FO_2Na$: 215.1, found: 215.1.

1-(2-Fluoro-1,1-dimethoxy-1,2-diphenylethane (2d)



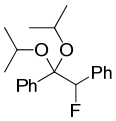
Following the general procedure A, compound **2d** was isolated in 92 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24-7.07 (m, 8H), 6.87 (d, J = 7.3 Hz, 2H), 5.73 (d, $J_{H\text{-}F}$ = 45.8 Hz, 1H), 3.56 (s, 3H), 3.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8 (d, $J_{C\text{-}F}$ = 20.2 Hz), 135.6, 128.5, 128.2, 128.0 (d, $J_{C\text{-}F}$ = 1.1 Hz), 127.3, 127.2, 127.0 (d, $J_{C\text{-}F}$ = 8.0 Hz), 102.8 (d, $J_{C\text{-}F}$ = 23.4 Hz), 93.1 (d, $J_{C\text{-}F}$ = 183.4 Hz), 49.6 (d, $J_{C\text{-}F}$ = 1.5 Hz), 49.5 (d, $J_{C\text{-}F}$ = 1.5 Hz). IR (film): $\tilde{\upsilon}$ = 2943, 2834, 2356, 1495, 1451, 1320, 1241, 1213, 1123, 1080, 1053, 983, 857, 715, 700 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{16}H_{17}FO_2Na$: 283.1104, found: 283.1106.

2-Fluoro-1,2-diphenylethanone (3d)[7]



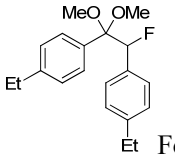
Following the general procedure B, compound **3d** was isolated in 80 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95-7.93 (m, 2H), 7.59-7.35 (m, 8H), 6.5 (d, $J_{H\text{-}F}$ = 48.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.0 (d, $J_{C\text{-}F}$ = 21.4 Hz), 135.2 (d, $J_{C\text{-}F}$ = 58.4 Hz), 134.5 (d, $J_{C\text{-}F}$ = 11.9 Hz), 134.3, 130.4, 130.1 (d, $J_{C\text{-}F}$ = 2.3 Hz), 129.6 (d, $J_{C\text{-}F}$ = 1.2 Hz), 129.3 (d, $J_{C\text{-}F}$ = 39.9 Hz), 127.9 (d, $J_{C\text{-}F}$ = 5.9 Hz), 94.4 (d, $J_{C\text{-}F}$ = 187.1 Hz).

1-(2-Fluoro-1,1-diisopropoxy-1,2-diphenylethane (4d)



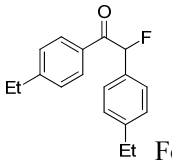
Following the general procedure C, compound **4d** was isolated in 84 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24-7.18 (m, 6H), 7.13-7.04 (m, 4H), 5.72 (d, $J_{H\text{-}F}$ = 45.3 Hz, 1H), 4.51 (sept, J = 6.1 Hz, 1H), 4.04 (sept, J = 6.3 Hz, 1H), 1.42 (dd, J = 1.0, 6.1 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.22 (d, J = 6.1 Hz, 3H), 0.90 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 136.8 (d, $J_{C\text{-}F}$ = 20.5 Hz), 131.6, 129.4, 127.8, 127.5 (d, $J_{C\text{-}F}$ = 8.8 Hz), 126.9, 126.3, 102.9 (d, $J_{C\text{-}F}$ = 26.4 Hz), 92.4 (d, $J_{C\text{-}F}$ = 181.9 Hz), 65.0, 64.0, 24.6, 24.5, 24.4 (d, $J_{C\text{-}F}$ = 2.9 Hz), 24.1. IR (film): $\tilde{\upsilon}$ = 2974, 2361, 2155, 2040, 1970, 1449, 1383, 1312, 1206, 1176, 1120, 1083, 1036, 943, 868, 709 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{20}H_{25}FO_2Na$: 339.1730, found: 339.1727.

1,2-bis(4-Ethylphenyl)-2-fluoro-1,1-dimethoxyethane (2e)



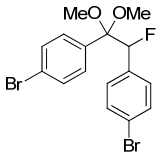
Following the general procedure A, compound **2e** was isolated in 73 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (s, 4H), 6.98 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 8.0 Hz, 2H), 5.68 (d, $J_{H\text{-}F}$ = 45.9 Hz, 1H), 3.53 (s, 3H), 3.23 (s, 3H), 2.65-2.56 (m, 4H), 1.23-1.17 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5, 144.3 (d, $J_{C\text{-}F}$ = 1.4 Hz), 133.4 (d, $J_{C\text{-}F}$ = 20.2 Hz), 133.3, 128.8 (d, $J_{C\text{-}F}$ = 1.1 Hz), 127.5 (d, $J_{C\text{-}F}$ = 7.3 Hz), 127.0, 126.0, 103.2 (d, $J_{C\text{-}F}$ = 23.8 Hz), 93.7 (d, $J_{C\text{-}F}$ = 182.6 Hz), 49.9 (d, $J_{C\text{-}F}$ = 1.4 Hz), 49.7 (d, $J_{C\text{-}F}$ = 1.4 Hz), 28.8, 28.8, 15.8, 15.7. IR (film): $\tilde{\upsilon}$ = 2965, 2834, 1513, 1458, 1178, 1122, 1064, 908, 840, 733, 671 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{20}H_{25}FO_2Na$: 339.1730, found: 339.1761.

1,2-bis(4-Ethylphenyl)-2-fluoroethanone (3e)



Following the general procedure B, compound **3e** was isolated in 68 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 7.9 Hz, 2H), 7.40 (dd, J = 1.3, 7.9 Hz, 2H), 7.24 (t, J = 8.2 Hz, 4H), 6.47 (d, $J_{H\text{-}F}$ = 48.7 Hz, 1H), 2.69-2.60 (m, 4H), 1.22 (t, J = 7.7 Hz, 3H), 1.21 (t, J = 7.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.3 (d, $J_{C\text{-}F}$ = 21.4 Hz), 151.3, 146.4 (d, $J_{C\text{-}F}$ = 2.9 Hz), 132.3, 132.1, 129.8 (d, $J_{C\text{-}F}$ = 2.3 Hz), 129.1, 128.6, 128.1 (d, $J_{C\text{-}F}$ = 5.3 Hz), 94.2 (d, $J_{C\text{-}F}$ = 183.5 Hz), 29.4, 29.1, 15.7, 15.5. IR (film): $\tilde{\upsilon}$ = 2966, 2932, 2874, 1695, 1606, 1512, 1457, 1415, 1264, 1228, 1182, 1062, 861, 733 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{18}H_{19}FONa$: 293.1312, found: 293.1313.

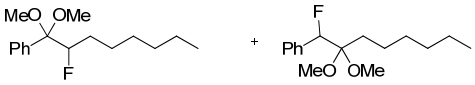
1,2-bis(4-Bromophenyl)-2-fluoro-1,1-dimethoxyethane (2f)



To a mixture of the 1,2-bis(4-bromophenyl)acetylene (0.1mmol, 1 equiv.) and selectfluor (0.2 mmol, 2 equiv.) in MeOH (1 mL), $Ph_3PauNTf_2$ (0.005mmol, 0.05equiv.) was added and the solution was stirred for 2h at 80 ^{0}C. Then, another 5% of catalyst was added and the mixture was stirred at the same temperature for 2h more. Upon reaction completion, the mixture was diluted with DCM and filtered under Celite. The solvent was evaporated under reduced pressure and the residue was purified by silica gel flash column chromatography (Pentane/diethyl ether = 20/1) to yield the compound **2f** in 85% yield ; ^{1}H

NMR (400 MHz, $CDCl_3$): δ = 7.32 (t, J = 8.5 Hz, 4H), 6.93 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 5.67 (d, $J_{H\text{-}F}$ = 45.1 Hz, 1H), 3.53 (s, 3H), 3.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.9 (d, $J_{C\text{-}F}$ = 22.0 Hz), 134.6, 130.8, 130.8 (d, $J_{C\text{-}F}$ = 1.1 Hz), 130.6 (d, $J_{C\text{-}F}$ = 1.1 Hz), 128.9 (d, $J_{C\text{-}F}$ = 8.1 Hz), 123.1, 122.6 (d, $J_{C\text{-}F}$ = 1.8 Hz), 102.7 (d, $J_{C\text{-}F}$ = 23.8 Hz), 92.8 (d, $J_{C\text{-}F}$ = 184.1 Hz), 49.8 (d, $J_{C\text{-}F}$ = 1.8 Hz), 49.7 (d, $J_{C\text{-}F}$ = 1.1 Hz). IR (film): $\tilde{\upsilon}$ = 2944, 2836, 1591, 1487, 1394, 1319, 1240, 1176, 1072, 1060, 1011, 835, 750, 734 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{16}H_{15}Br_2FONa$: 438.9315, found: 438.9311.

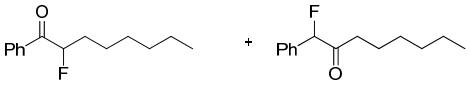
1-(2-Fluoro-1,1-dimethoxyoctyl)benzene (2g) and 1-(1-Fluoro-2,2-dimethoxyoctyl)benzene (2g')



2g **2g'**

Following the general procedure A, compounds **2g** and **2g'** were obtained as a mixture 10:1 respectively in 72 % yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48-7.32 (m, 10H$_{major\ and\ minor}$), 5.51 (d, $J_{H\text{-}F}$ = 45.1 Hz, 1H$_{minor}$), 4.68 (dd, J = 9.4 Hz $J_{H\text{-}F}$ =49.0 Hz, 1H$_{major}$), 3.38 (s, 6H minor), 3.22 (s, 3H$_{major}$), 3.15 (s, 3H$_{major}$), 1.54-0.82 (m, 24H$_{major\ and\ minor}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.2, 137.0 (d, $J_{C\text{-}F}$ = 19.7 Hz), 128.8, 128.4 (d, $J_{C\text{-}F}$ = 22.5 Hz), 128.3 (d, $J_{C\text{-}F}$ = 16.7 Hz), 128.1, 127.2, 126.9 (d, $J_{C\text{-}F}$ = 8.3 Hz), 102.5 (d, $J_{C\text{-}F}$ = 19.7 Hz), 102.0 (d, $J_{C\text{-}F}$ = 22.6 Hz), 94.4 (d, $J_{C\text{-}F}$ = 181.8 Hz), 93.5 (d, $J_{C\text{-}F}$ = 181.8 Hz), 50.0 (d, $J_{C\text{-}F}$ = 1.7 Hz), 49.6, 49.3, 48.8, 38.9, 37.5, 32.6, 31.9, 31.8, 30.3, 30.2, 30.0, 29.2, 25.8, 22.8, 14.2.

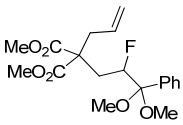
1-Phenyl-3-fluorooctanone (3g) and 1-phenyl-2-fluorooctanone (3g')



3g **3g'**

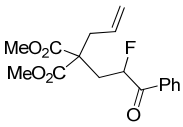
Following the general procedure B, compounds **3g** and **3g'** were obtained as a mixture 10:1 respectively in 80 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 7.7 Hz, 4H$_{major\ and\ minor}$), 7.62-7.39 (m, 6H$_{major\ an\ minor}$), 5.68 (d, $J_{H\text{-}F}$ = 48.9 Hz, 1H$_{minor}$), 5.55 (ddd, J = 2.2, 5.4 Hz $J_{H\text{-}F}$ = 49.5 Hz, 1H$_{major}$), 2.60-2.52 (m, 2H$_{minor}$), 2.02-0.82 (m, 22H$_{major\ and\ minor}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2 (d, $J_{C\text{-}F}$ = 18.4 Hz) (2C=O), 134.7 (d, $J_{C\text{-}F}$ = 1.2 Hz), 133.9, 129.5 (d, $J_{C\text{-}F}$ = 1.2 Hz), 129.2, 129.1, 129.1, 129.0, 126.3 (d, $J_{C\text{-}F}$ = 6.5 Hz), 96.1 (d, $J_{C\text{-}F}$ = 187.7 Hz), 95.1 (d, $J_{C\text{-}F}$ = 183.6 Hz), 37.7, 33.1 (d, $J_{C\text{-}F}$ = 21.4 Hz), 31.8, 31.7, 29.1, 28.9, 25.0 (d, $J_{C\text{-}F}$ = 2.9 Hz), 23.0 (d, $J_{C\text{-}F}$ = 1.2 Hz), 22.8, 22.7, 14.3, 14.2. IR (film): $\tilde{\upsilon}$ = 3063, 2954, 2928, 2857, 1727, 1698, 1597, 1579, 1495, 1449, 1377, 1277, 1232, 1182, 1136, 1277, 1182, 1139, 1026, 736 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{19}FONa$: 245.1312, found: 245.1310.

Dimethyl 2-allyl-2-(2-fluoro-3,3-dimethoxy-3-phenylpropyl)malonate (2h)



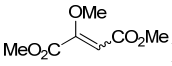
Following the general procedure A, compound **2h** was isolated in 86 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.46 (m, 2H), 7.38-7.32 (m, 3H), 5.44-5.34 (m, 1H), 4.96-4.78 (m, 3H), 3.62 (s, 3H), 3.61 (s, 3H), 3.36 (d, J = 1.5 Hz, 3H), 3.22 (s, 3H), 2.67-2.56 (m, 2H), 2.16 (ddd, J = 1.5, 15.6 Hz, $J_{H\text{-}F}$ = 42.3 Hz, 1H), 1.87 (dt, J = 10.0, 15.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 171.3, 136.8, 132.1, 128.7, 128.3, 128.2, 119.7, 102.1 (d, $J_{C\text{-}F}$ = 18.4 Hz), 91.6 (d, $J_{C\text{-}F}$ = 186.5 Hz), 55.7, 52.8, 52.6, 50.3 (d, $J_{C\text{-}F}$ = 2.3 Hz), 49.8, 37.8, 33.4 (d, $J_{C\text{-}F}$ = 19.7 Hz). IR (film): $\tilde{\upsilon}$ = 2943, 2834, 1736, 1436, 1289, 1205, 1141, 1080, 1052, 705 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{19}H_{25}FO_6Na$: 391.1527, found: 391.1524.

Dimethyl 2-allyl-2-(2-fluoro-3-oxo-3phenylpropyl)malonate (3h)



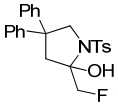
Following the general procedure D, compound **3h** was isolated in 99 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 7.4 Hz, 2H), 7,62-7.58 (m, 1H), 7.49 (t, J = 7.4 Hz, 2H), 5.87 (ddd, J = 2.1, 10.3 Hz, $J_{H\text{-}F}$ = 49.7 Hz, 1H), 5.58-5.58 (m, 1H), 5.19-5.12 (m, 2H), 3.77 (s, 3H), 3.66 (s, 3H), 2.88-2.77 (m, 2H), 2.67-2.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 195.4, 171.2 (d, $J_{C\text{-}F}$ = 13.6 Hz), 134.2, 134.0, 131.9, 129.3 (d, $J_{C\text{-}F}$ = 2.9 Hz), 120.1, 120.4, 90.4 (d, $J_{C\text{-}F}$ = 181.9 Hz), 55.7, 53.1, 52.9, 38.7, 36.1 (d, $J_{C\text{-}F}$ = 20.5 Hz). IR (film): $\tilde{\upsilon}$ = 2952, 2357, 2327, 1733, 1698, 1597, 1436, 1219, 1099, 931, 701 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{17}H_{19}FO_5Na$: 345.1108, found: 345.1107.

Dimethyl 2-methoxymaleate (5i)[8]



Following the general procedure, compound **5i** was isolated as a isomeric mixture (3:1 *Z:E*) in 84 % yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.21 (s, 1H), 3.89 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 164.2, 162.7, 93.4, 57.2, 53.2, 51.9.

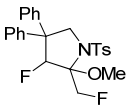
2-(Fluoromethyl)-4,4-diphenyl-1-tosylpyrrolidin-2-ol (7)



To a solution of **6** (49 mg, 0.125 mmol, 1 equiv.) in MeCN/H_2O (20:1) (6.25 mL, 0.02 M), were added $NaHCO_3$ (10 mg, 0.125 mmol, 1 equiv.) and Selectfluor (90 mg, 0.25 mmol, 2 equiv.). The solution was refluxed at 80 ^{0}C and monitored by TLC. Upon

completion, the mixture was poured on H_2O (1 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, concentrated under vacuum and purified by flash column chromatography (80 % Hexane/AcOEt) to afford the corresponding pyrrolidinol **7** (42.5 mg, 0.1 mmol) in 80 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.1 Hz, 2H), 7.24-7.11 (m, 12H), 4.52 (dd, $J_{H\text{-}F}$ = 46.9 Hz, $J_{H\text{-}H}$ = 9.2 Hz, 1H), 4.18 (dd, $J_{H\text{-}F}$ = 46.9 Hz, $J_{H\text{-}H}$ = 9.2 Hz, 1H), 3.99 (d, J = 9.9 Hz, 1H), 3.92 (d, J = 9.9 Hz, 1H), 3.07 (dd, J = 2.1, 13.3 Hz, 1H), 2.79 (dd, J = 13.3 Hz, 1H), 2.37 (s, 3H,), 1.54 (bs, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 144.3, 136.6, 130.2, 129.2, 129.1, 128.2, 127.3, 127.2, 127.0, 126.9, 93.1 (d, $J_{C\text{-}F}$ = 22.3 Hz), 84.8 (d, $J_{C\text{-}F}$ = 178.2 Hz), 57.5, 51.2, 48.1, 22.0. (An aromatic carbon is overlapped). IR (film): $\tilde{\upsilon}$ = 3493, 2920, 1597, 1495, 1448, 1330, 1161, 1088, 1011, 911, 750, 701, 666 cm^{-1}. HRMS (ESI): *m/z*: calcd for $C_{24}H_{24}FNO_3SNa$: 448.1353 found: 448.1357.

2-(Fluoromethyl)- 3-fluoro-2-methoxy-4,4-diphenyl-1-tosylpyrrolidine (7')



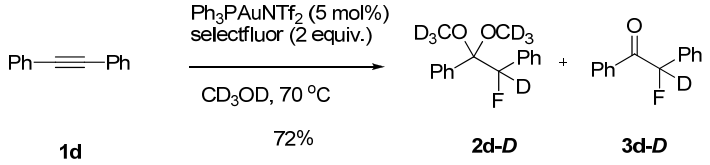
To a solution of **6** (49 mg, 0.125 mmol, 1 equiv.) in MeOH (6.25 mL, 0.1 M), was added Selectfluor (90 mg, 0.25 mmol, 2 equiv.). The solution was refluxed at 70 ^{0}C and monitored by TLC. The reaction was completed in 1 h and the mixture was filtered through a short pad of Celite, concentrated under vacuum and purified by flash column chromatography (95 % Hexane/AcOEt) to afford the corresponding pyrrolidine **7'** (42.5 mg, 0.1 mmol) in 70 % yield as a diasteroisomeric mixture in a ratio 2:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.7 Hz, 2H$_{minor}$), 7.72 (d, J = 8.7 Hz, 2H$_{major}$), 7.25-7.05 (m, 24H$_{major\ and\ minor}$), 5.63 (d, $J_{H\text{-}F}$ = 50.5 Hz, 1H$_{major}$), 5.61 (dd, $J_{H\text{-}F}$ = 50.5 Hz, $J_{H\text{-}H}$ = 1.1 Hz, 1H$_{minor}$), 5.16 (dd, $J_{H\text{-}F}$ = 48.2 Hz, $J_{H\text{-}H}$ = 4.5 Hz, 1H$_{major}$), 4.67 (dd, $J_{H\text{-}F}$ = 48.2 Hz, $J_{H\text{-}H}$ = 1.5 Hz, 1H$_{minor}$), 4.62-4.45 (m, 2H$_{major\ and\ minor}$), 4.37 (dd, J = 9.9, 3.1 Hz, 1H$_{minor}$), 4.28 (dd, J = 7.7, 1.5 Hz, 1H$_{major}$), 4.06-4.00 (m, 1H$_{major}$), 3.60 (d, J = 9.9 Hz, 1H$_{minor}$), 3.10 (s, 3H$_{major}$), 3.07 (s, 3H$_{minor}$), 2.36 (s, 3H$_{major}$), 2.34 (s, 3H$_{minor}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.8, 144.6, 143.5, 142.2 (d, $J_{C\text{-}F}$ = 3.5 Hz), 141.4, 140.1, 136.2, 136.1, 130.3, 130.1, 129.6, 129.0, 128.9, 128.8, 128.7, 128.6, 128.6, 128.1, 127.8, 127.5, 127.4, 127.2, 127.0, 126.9, 98.8 (d, $J_{C\text{-}F}$ = 198.4 Hz), 97.9 (dd, $J_{C\text{-}F}$ = 26.1, 25.0 Hz), 94.9 (d, $J_{C\text{-}F}$ = 208.0 Hz), 93.8 (dd, $J_{C\text{-}F}$ = 20.1, 21.0 Hz), 82.5 (d, $J_{C\text{-}F}$ = 177.6 Hz), 80.7 (dd, $J_{C\text{-}F}$ = 177.8, 7.7 Hz), 56.7, 55.1 (d, $J_{C\text{-}F}$ = 17.7 Hz), 54.0, 53.8, 53.5, 51.9 (d, $J_{C\text{-}F}$ = 2.9Hz), 22.1 (x 2C). IR (film): $\tilde{\upsilon}$ = 3025, 2956, 1598, 1496, 1449, 1348, 1163, 1088, 1022, 911, 814, 734, 701 cm^{-1}.

6.5 Supplementary data

6.5.1 Further experiments with substrates diphenylacetylene (1d) and *N*-(2,2-Diphenylpent-4-ynyl)-4-methylbenzenesulfonamide (6)

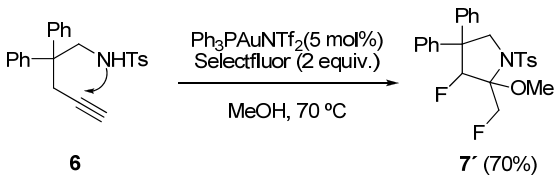
The reaction of **1d** was also performed in CD_3OD. As expected for a reaction proceeding via enolether (see **III** in Scheme 6 in the article), deuterium was incorporated in the Cα to the acetal or the ketone moiety.

Scheme 8. Labeling experiments



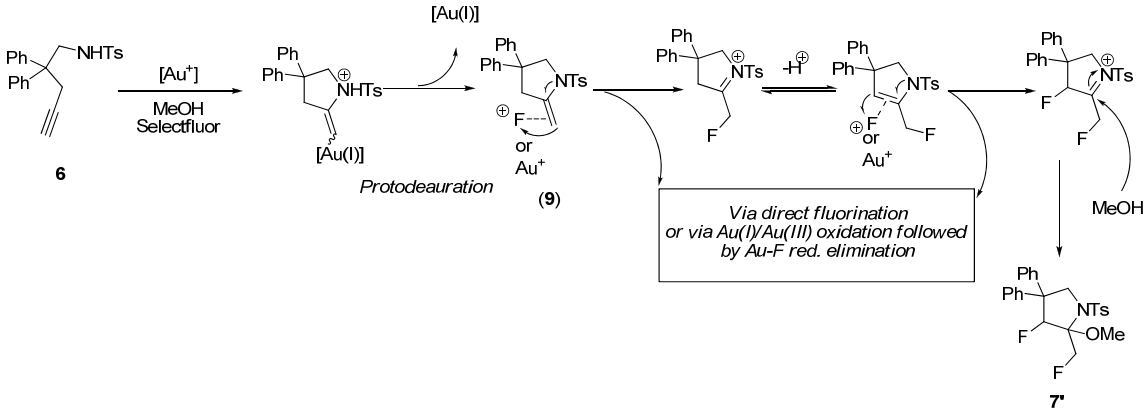
The reaction of tosylamide **6** under the standard reaction conditions afforded bis-fluorinated product **7´**.

Scheme 9. Synthesis of bis-fluorinated product **7'**.



Several mechanisms can be proposed to justify the the formation of **7´** product: upon nucleophilic attack of the nitrogen onto the gold-activated alkyne and protodeauration, an enamine (**9**) should be obtained. As discussed already in the article, either Selectfluor itself but also gold(I) to some extent could reactivate the electron-rich double bond triggering the formation of the new Csp^3-F bond either by direct fluorination or via Selectfluor oxidation of gold(I) to gold(III) and reductive elimination. The iminium formed can be in equilibrium with an enamine form, which undergoes the same type of re-activation/fluorination reaction to form the second Csp^3-F bond. Finally, the last iminium cation is attacked by a molecule of MeOH to give product **7´**as a 1:2 mixture of diastereoisomers.

Scheme 10. Mechanism proposal for the synthesis of bis-fluorinated product **7'**



6.6. References

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Chapter 7

Conclusion and Outlook

CHAPTER 7

Conclusion and Outlook

Over the past decades, gold has been recognized as a powerful Lewis acid able to activate unsaturated moieties triggering a wide palette of transformations. In contrast to other transition metals, the most significant limitation of homogeneous gold catalysis seemed to be the inferior ability of gold to change oxidation state during catalytic cycles. The work summarized in this thesis, together with key contributions from other research groups has helped to reverse this paradigm. We have demonstrated that when reacted in the presence of strong external oxidants, gold(I)/gold(III) redox catalytic cycles become accessible leading to coupling reactions involving the formation of new C-C or C-X (X = Heteroatom) bonds.

In this thesis, we present a gold-catalyzed cross coupling reaction of electron rich arenes and electron deficient alkynes using a $PhI(OAc)_2$ as external oxidant; this reaction hold promise as elegant alternative to palladium-catalyzed Sonogashira reaction, removing the requirement to pre-activate the arene starting material prior to coupling. Detailed mechanistic work focused on elucidating each individual step along the catalytic cycle was investigated. In depth kinetic studies revealed that the rate limiting state in this transformation is the oxidation of gold(I) species to gold(III) productive intermediates. Furthermore, KIE showed that the formation of Csp^2-Au bond occurs by electrophilic aromatic substitution rather than Csp^2-H activation process.

Additionally, gold-catalyzed nucleophilic additions onto activated C-C triple and double bond followed by an oxidative coupling based on gold(I)/gold(III) redox catalytic cycles has been successfully demonstrated, replacing the protodeauration step typically observed in gold-catalyzed alkyne, allene or alkene hydrofunctionalization reactions. These cascades process allow a rapid construction of molecular complexity in a single transformation.

Building up on this concept, we have discovered a flexible gold-catalyzed difunctionalization of unactivated olefins where both, the ability of gold to activate unsaturated moieties and its redox catalytic cycle for the formation of new C-C, C-O and C-N bonds were synergistically combined. Thus, 1,3-aminoalcohols, aminoethers and aminoamides could be efficiently obtained with this methodology. In addition, the synthesis of tricycle benzacepines was efficiently achieved in a diasteromerically pure form as a result of gold-catalyzed oxidative arylation reaction.

Due to the importance of fluorinated compounds in medicinal chemistry, pharmacology and medicine, we decide to study gold-catalyzed fluorinations on unsaturated molecules. An

efficient synthesis of α-fluoroenones based on a tandem gold-catalyzed 1,3-OAc migration followed by fluorination starting from propargyl acetates and α-fluoroacetal or α-fluoroketones from alkynes using selectfluor as stoichiometric source of fluorine were successfully developed.

The combination of oxidation/reduction chemistry of gold with its unique ability to act as a mild π Lewis acid promises enormous potential from a synthetic point of view. However, further understanding of the mechanistic insight governing the individual steps of the catalytic cycle will be needed in order to accelerate the development of new transformations. Such studies may shed light on the factors affecting the relative rates of coupling and undesired protodeauration-based side reactions allowing for more enlightened selection of reaction conditions. In addition, greater control over the selectivity of coupling processes in favor of cross-coupled products over homodimers of each coupling partner may be possible and will open up new pathways to tackle unprecedented transformation aiming to increase molecular complexity. A desirable extension of this chemistry involves the development of asymmetric catalysis by using chiral ligands on gold or by introducing chirality in the external oxidant. Therefore, a lot of research in this promising area of catalysis is waiting to be done before gold catalysts will truly get their place as a versatile tool for cross coupling reactions.

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9. *"Synthetic Potential behind gold-catalyzed redox processes"* T. de Haro, C. Nevado *New Strategies in Chemical Synthesis and Catalysis* **2011**, Wiley-VCH (Ed. Bruno Pignataro). (Book Chapter)

8. *"Gold-catalyzed C-H activation processes''* T. de Haro, C. Nevado* *Synthesis* **2011**, *16*, 2530-2539.

7. *"Flexible Gold-Catalyzed Regioselective Oxidative Difunctionalization of Unactivated Alkenes"* T. de Haro, C. Nevado* *Angew. Chem. Int. Ed.* **2011**, *50*, 906–910.

6. *"Gold Catalyzed Synthesis of α-Fluoroacetals and α-Fluoro-ketones from Alkynes"* T. de Haro, C. Nevado* *Adv. Synth. Catal.* **2010**, *352*, 2767–2772.

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Poster Presentation / Conferences

Oct. 2011 **6th Dorothy Crowfoot Hodgkin Interdisciplinary Symposium**, ***UZH, Zürich***
Poster: *"Flexible Gold-Catalyzed Regioselective Oxidative Difunctionalization of Unactivated Alkenes"* T. de Haro, and C. Nevado

July 2011 **OMCOS 16th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis**, ***Shanghai, China***
Poster: *"Flexible Gold-Catalyzed Regioselective Oxidative Difunctionalization of Unactivated Alkenes"* T. de Haro, and C. Nevado

Nov. 2010 **5th Dorothy Crowfoot Hodgkin Interdisciplinary Symposium**, ***UZH, Zürich***
Poster: *"Gold Catalyzed Ethynylation of Arenes"*, T. de Haro, and C. Nevado

Sept. 2010 **Swiss Chemical Society (SCS) Fall Meeting 2010**, ETH-Zürich
Lecture: *"Gold Catalyzed Ethynylation of Arenes"* T. de Haro, and C. Nevado

July. 2009 **10th Tetrahedron Symposium**, ***Paris, France***
Poster: *"Gold-Catalyzed Stereocontrolled Synthesis of 2,3-Bisacetoxy-1,3-Dienes"* T. de Haro, X. Huang, and C. Nevado.

Sept. 2006 **XXI Biannual Meeting of Organic Chemistry of the Royal Spanish Chemical Society (RSEQ)**, ***Valladolid, Spain***
Lecture: *"Asymmetric Aza-Henry Reactions of N-p-Tolylsulfinylimines with nitroalkanes and posterior transformation in high interesting compounds"*, J. L. García Ruano, T. de Haro, J. López-Cantarero, R. Singh, J. Alemán, M. Toop, M. J. Remuiñán, M. B. Cid.

Awards

- PhD Research Grant delivered by Autónoma University–Lilly S.A. (Jan.–Jul. 2007)
- Poster award at the 5th Dorothy Crowfoot Hodgkin Interdisciplinary Symposium, Zürich, Nov. 2010
- 2011 CMSZH Travel Award sponsored by Büchi Labortechnik (April 2011)
- 2011 SCNAT/SCS Chemistry Travel Award (May 2011)
- Poster award at the 6th Dorothy Crowfoot Hodgkin Interdisciplinary Symposium, Zürich, Oct. 2011